



Trasduzione del segnale:

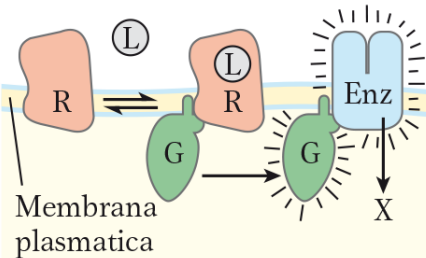
- canali ionici controllati
- recettori accoppiati alle proteine G (GPCRs)

Michele Sallese

Canali ionici controllati

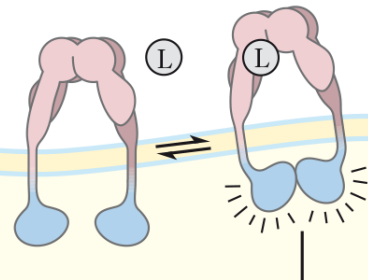
1. Recettori accoppiati alle proteine G

Il legame di un ligando esterno (L) al recettore (R) attiva una proteina intracellulare che lega il GTP (G); essa a sua volta regola l'attività di un enzima (Enz), che genera un secondo messaggero intracellulare (X).



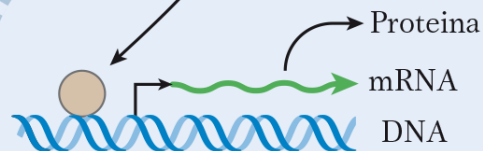
2a. Recettore con attività tirosina chinasi

Il legame del ligando innesca l'attività tirosina chinasi mediante autofosforilazione.



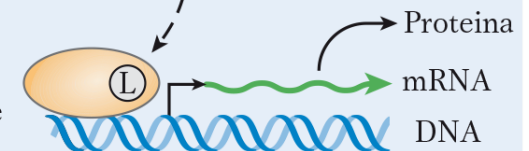
2b. La chinasi attiva un fattore di trascrizione, alterando l'espressione genica.

Membrana nucleare



Proteina
mRNA
DNA

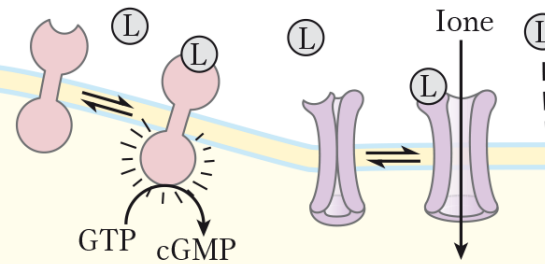
6. Recettore nucleare
Il legame dell'ormone permette al recettore di regolare l'espressione di geni specifici.



Proteina
mRNA
DNA

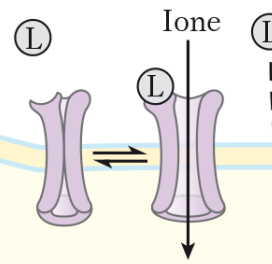
3. Recettore con attività guanilil ciclasica

Il legame del ligando al dominio extracellulare stimola la formazione del secondo messaggero, il GMP ciclico (cGMP).



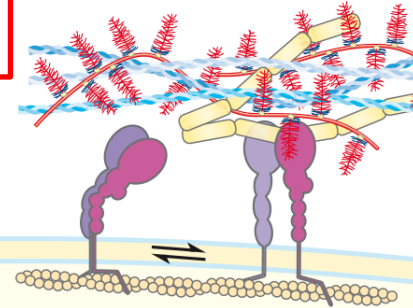
4. Canale ionico controllato

Si apre e si chiude in risposta alla concentrazione del ligando segnale o al potenziale di membrana.



5. Recettore di adesione (integrina)

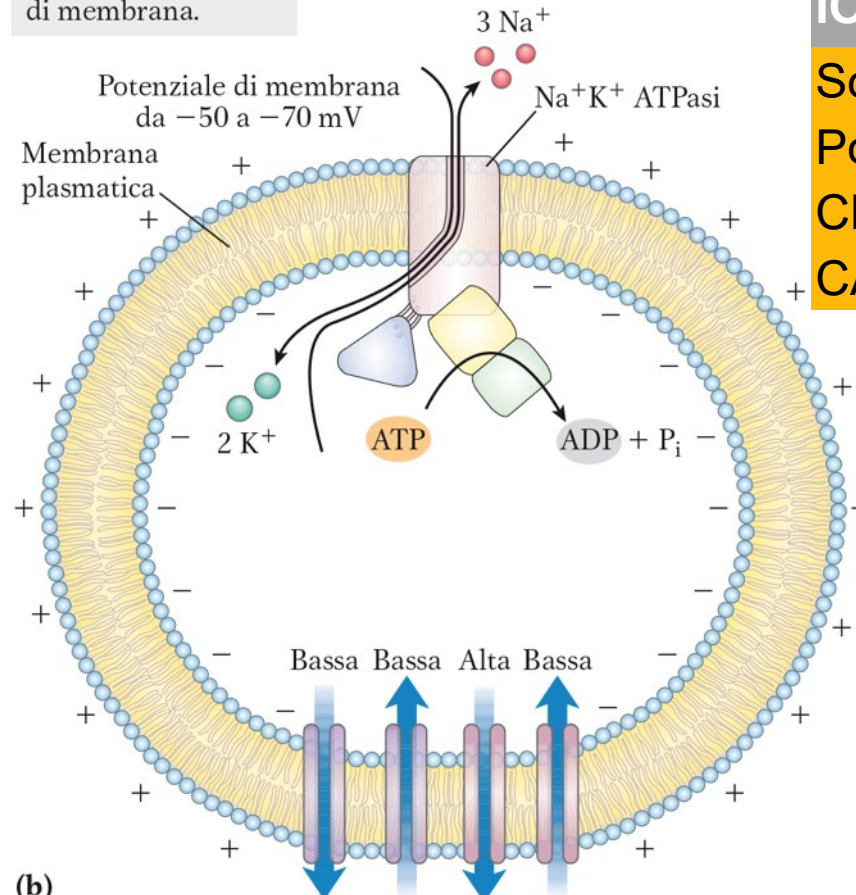
Legna molecole della matrice extracellulare, cambia la propria conformazione e altera l'interazione con il citoscheletro.



Canali ionici controllati

(a)

La Na^+K^+ ATPasi elettrogenica genera un potenziale di membrana.



(b)

Gli ioni tendono a muoversi attraverso una membrana polarizzata in favore del gradiente elettrochimico.

IONE	CONCENTRAZIONE INTRACELLULARE	CONCENTRAZIONE EXTRACELLULARE
Sodio	15mM	145 mM
Potassio	150mM	4mM
CLORO	5mM	120 mM
CALCIO	10-7m	2mM

L'attivazione di canali ionici produce segnali elettrici cioè una variazione del potenziale di membrana

I canali ionici sono controllati da:

- ligando
- voltaggio

I RECETTORI-CANALE SONO SELETTIVI PER CARICA

In base alla carica che lasciano passare i recettori-canale si dividono in:

1- cationici: fanno passare **cariche positive** come sodio e

Calcio; esempio recettori per

l'acetilcolina,

il glutammato,

le purine,

la serotonina

i nucleotidi ciclici

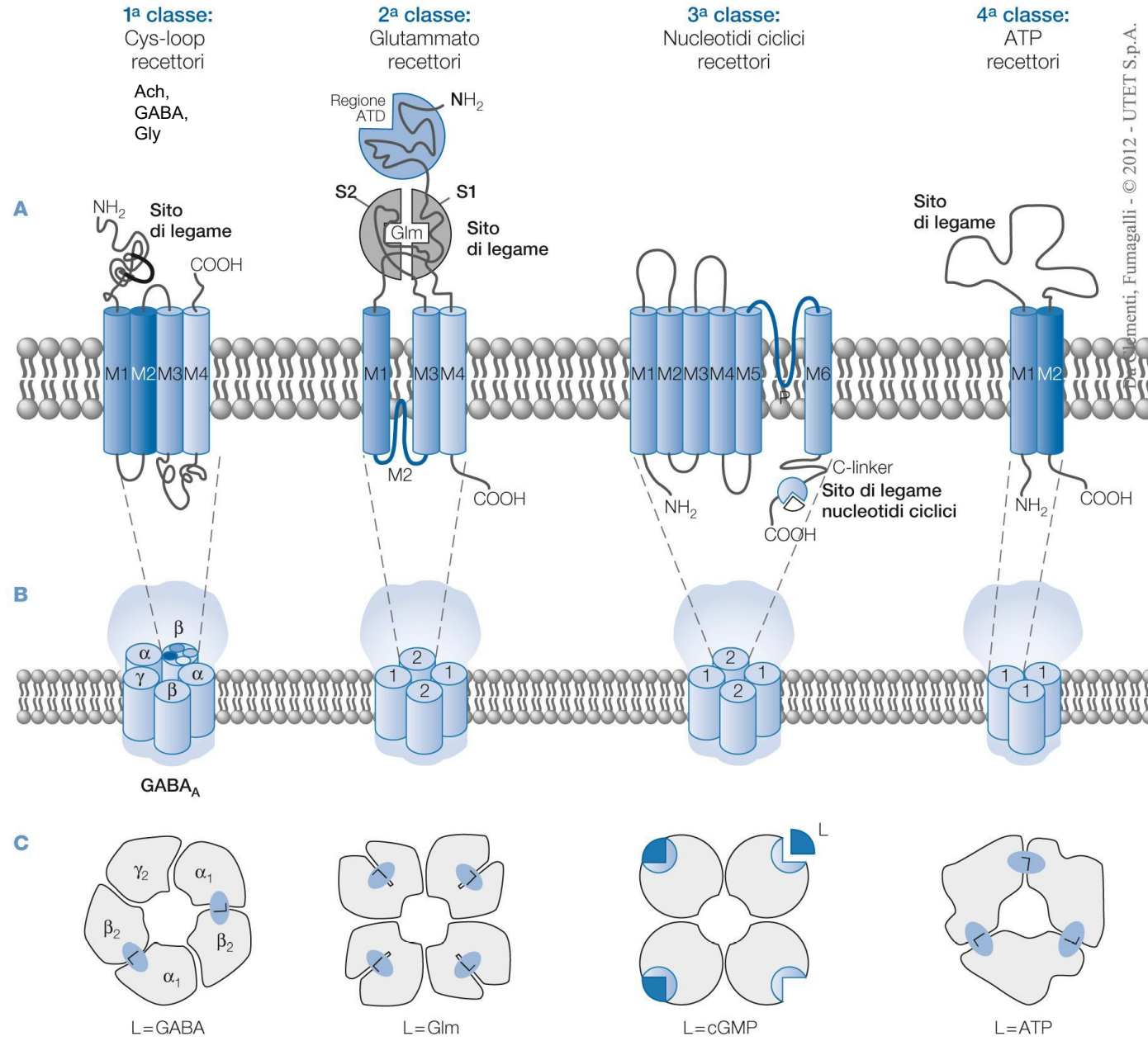
2- anionici: fanno passare **cariche negative** come cloro;

Esempio recettore per

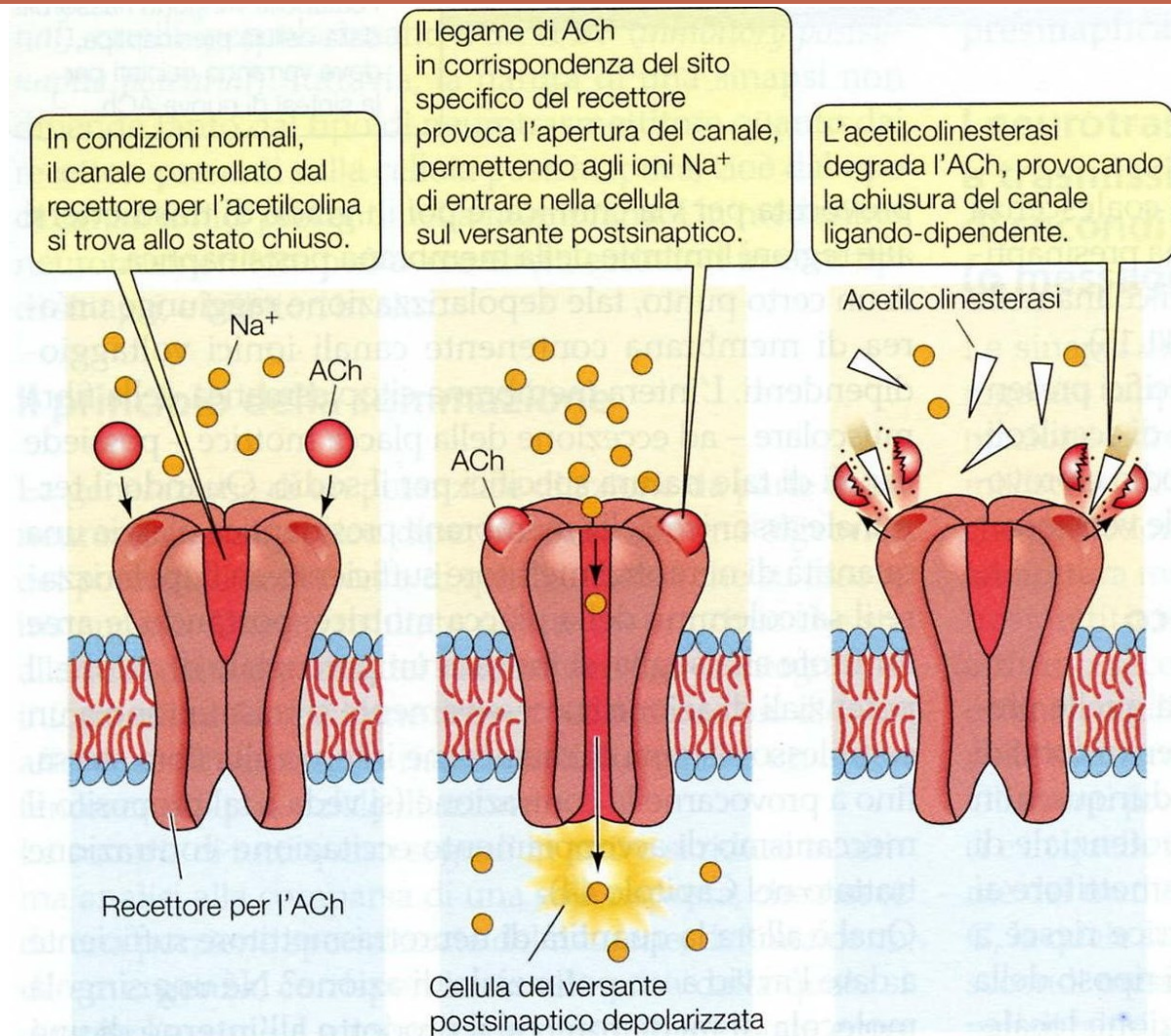
il GABA,

la glicina

Struttura molecolare dei recettori-canale

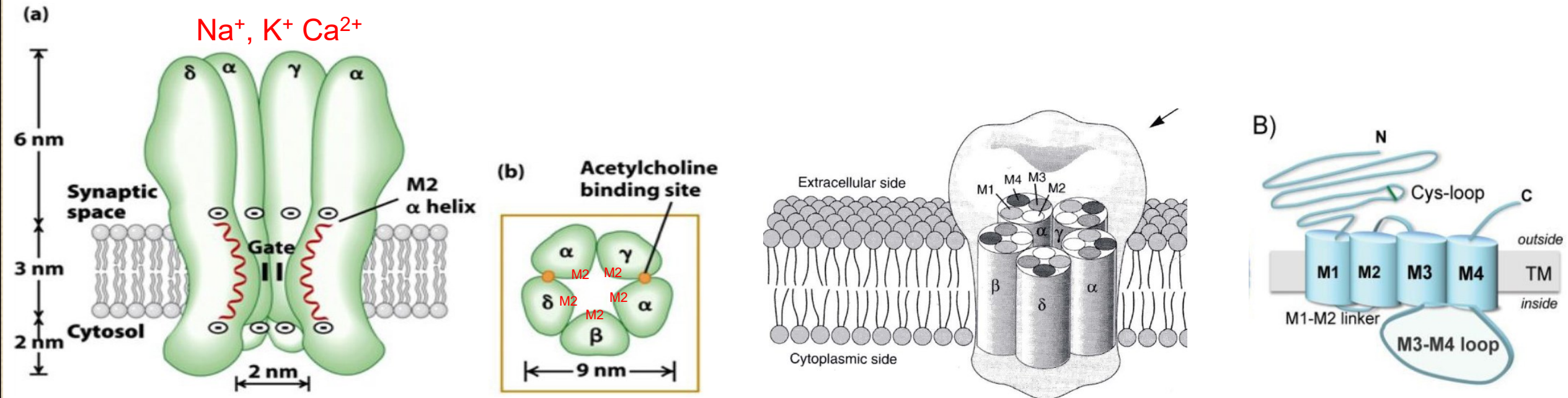


Recettore-canale attivato da ligando (acetil colina)



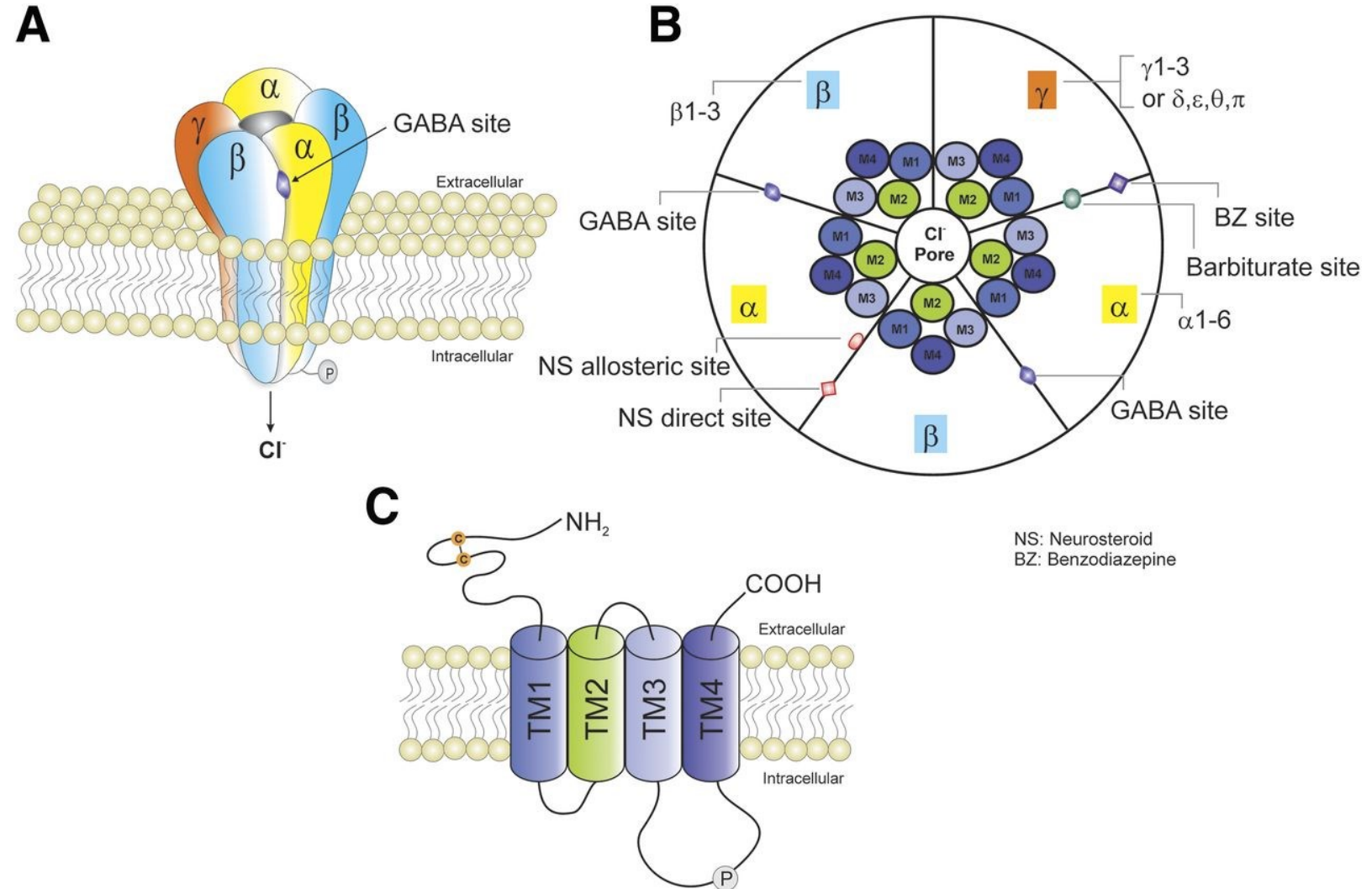
Recettore-canale attivato da ligando (acetil colina)

Il recettore muscolare è costituito da 5 subunità ($\alpha_2\beta\gamma\delta$)
Ciascuna con 4 eliche (M1-M4) transmembrana

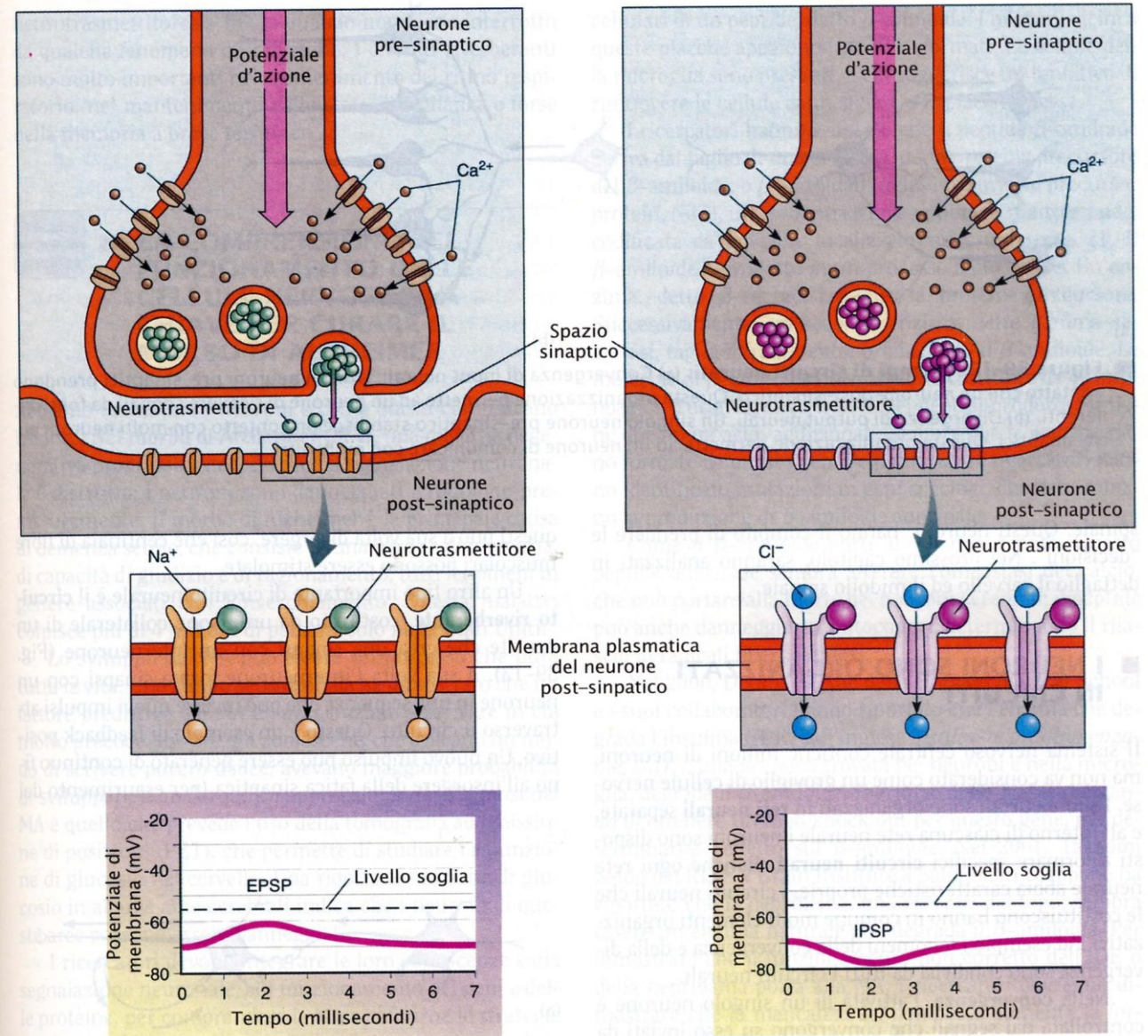


Quando due molecole di acetilcolina si legano alla subunità alfa del recettore, si apre un canale ionico che permette il passaggio all'interno della cellula di ioni Na^+ e Ca^{++} con conseguente depolarizzazione ed eccitazione cellulare.

Recettore-canale attivato da ligando (GABA)



A seconda della carica permeante, la stimolazione recettoriale può portare a depolarizzazione o iperpolarizzazione



(a) Input eccitatorio

(b) Input inibitorio

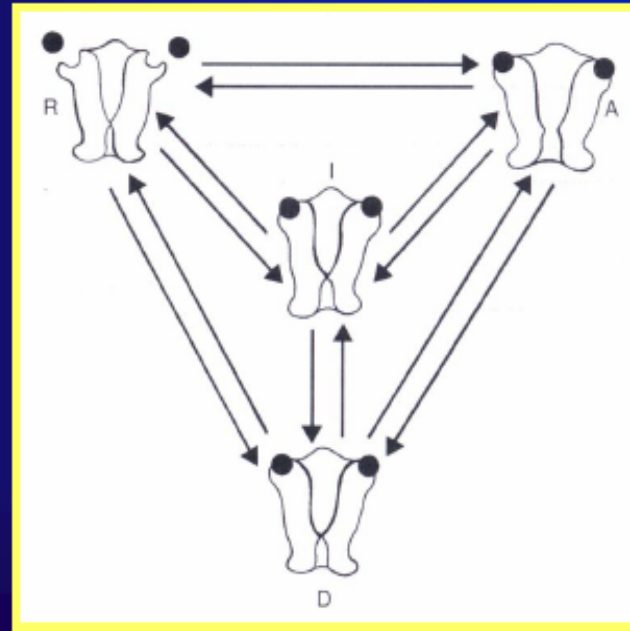
■ **Figura 39-11 Confronto tra (a) un potenziale post-sinaptico eccitatorio (EPSP) e (b) un potenziale post-sinaptico inibitorio (IPSP).** Da notare che un neurotrasmettore, che apre i canali per il Na^+ genera EPSP. Questo porta alla genesi di un potenziale d'azione. Un neurotrasmettore che apre i canali per il Cl^- genera IPSP e in questo modo iperpolarizza la membrana.

DESENSITIZZAZIONE DEI RECETTORI CANALE

Per questa superfamiglia di recettori la desensitizzazione equivale a una riduzione della capacità di andare incontro alle modificazioni conformazionali necessarie per produrre l'apertura del canale ionico.

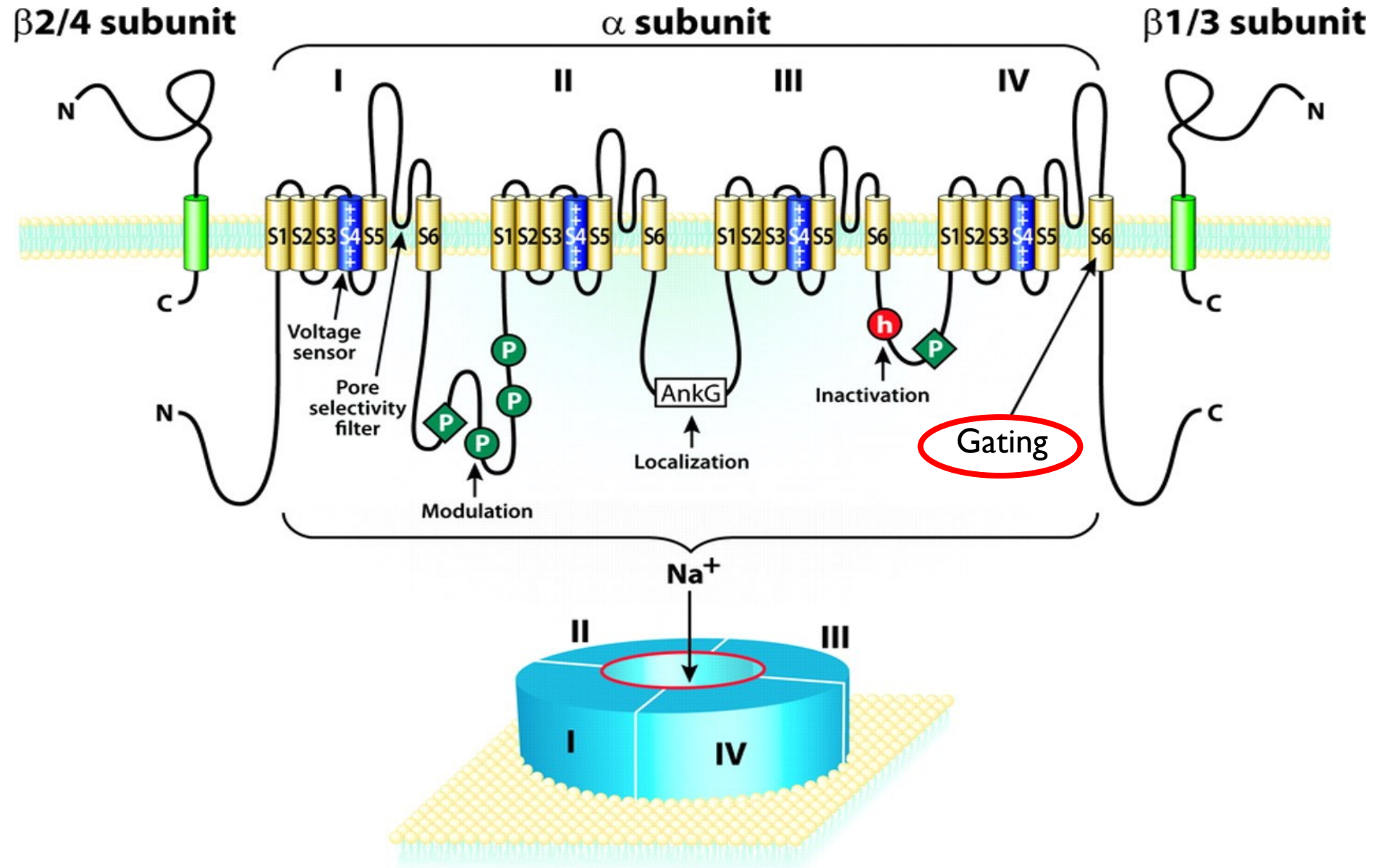
Applicazione AGONISTI e loro legame al recettore:

- 1) dopo pochi msec apertura del canale e flusso ionico (A)
- 2) successivamente transizione del R nello stato desensitizzato: il canale rimane chiuso nonostante l'affinità per l'agonista aumenti notevolmente (I e D)

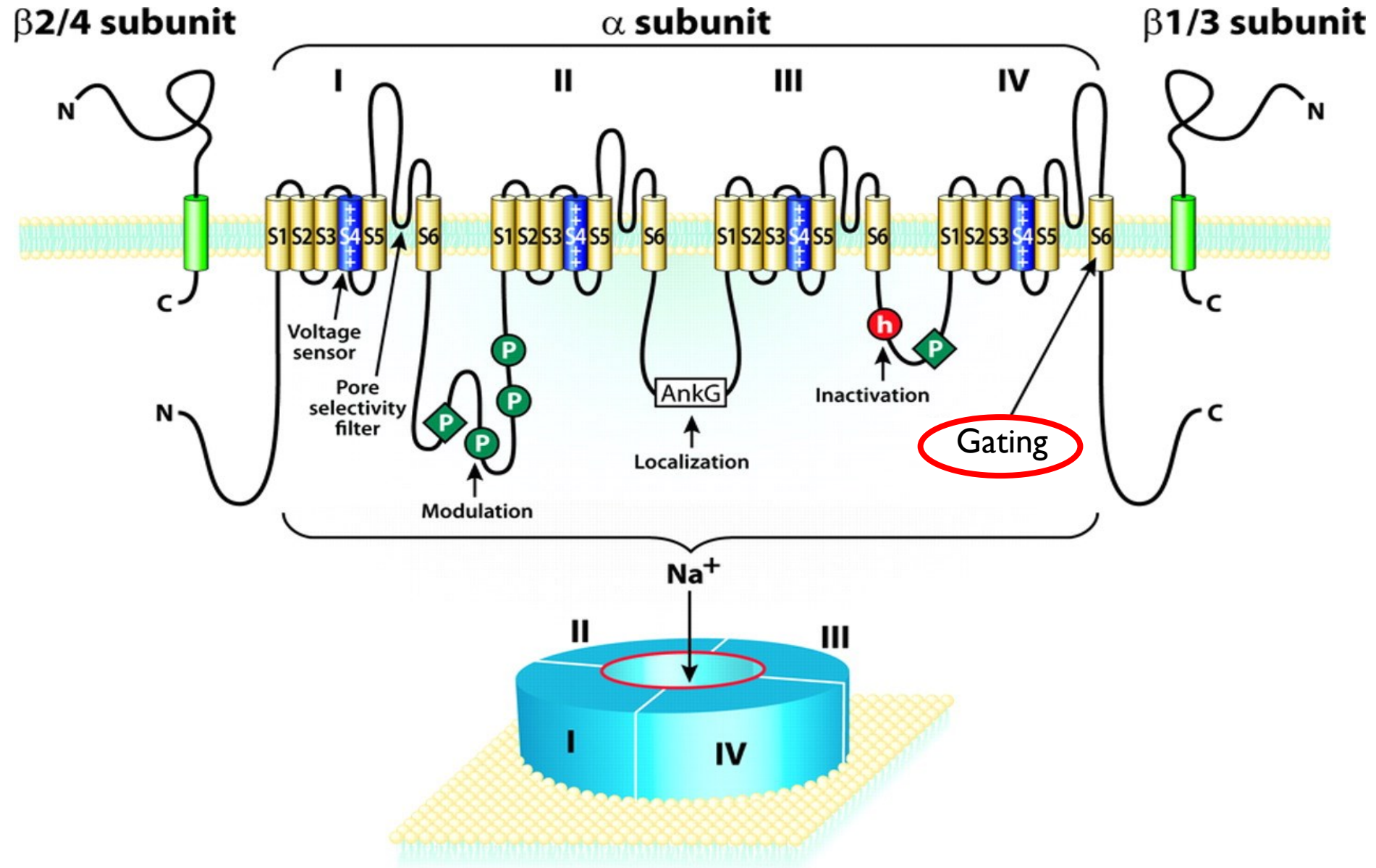


R= a riposo;
A= stato attivo;
I= componente rapida della desensitizzazione (stato desensitizzato);
D= componente lenta della desensitizzazione (stato refrattario)

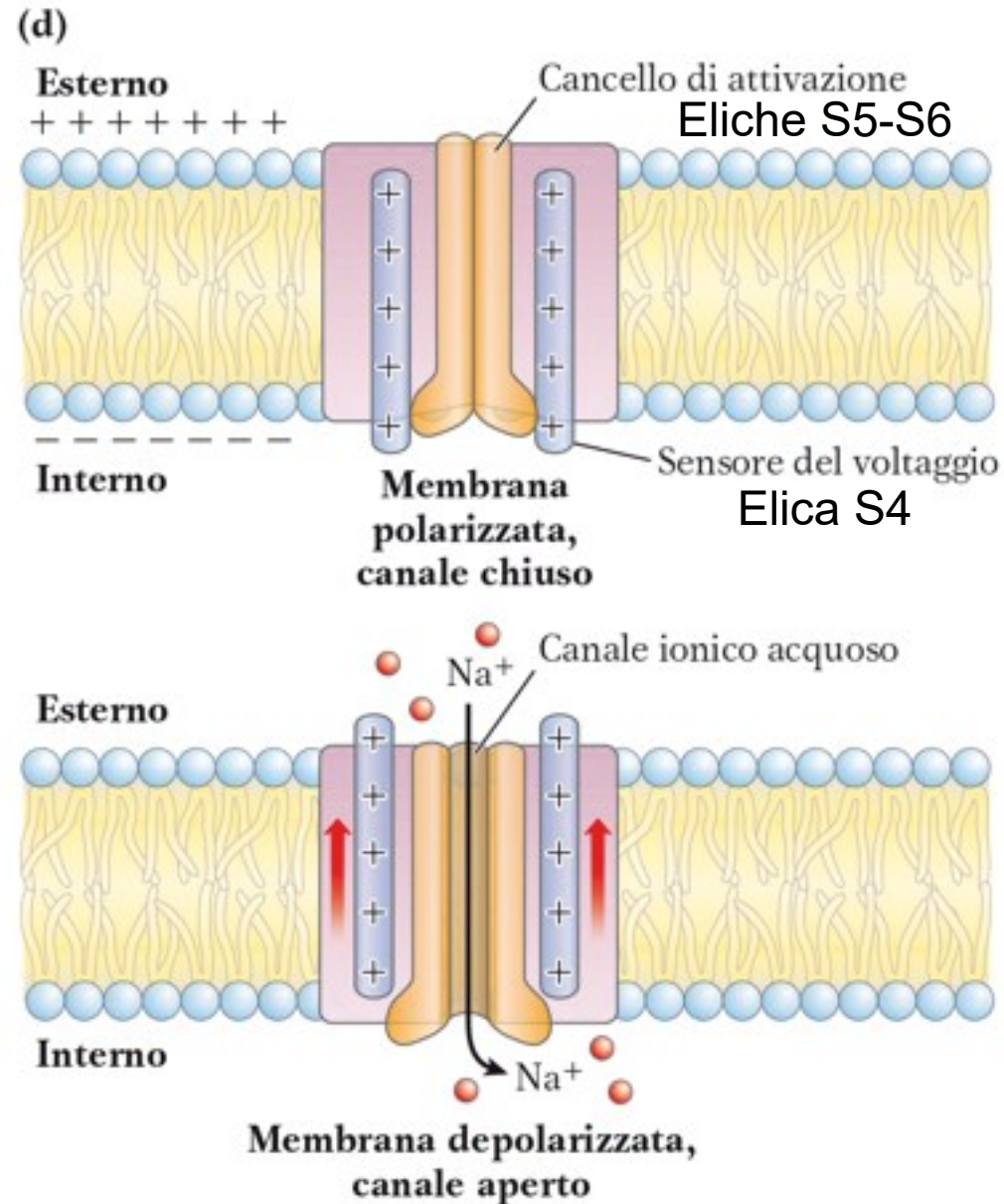
Canale del Na⁺ **v**oltaggio dipendente



Canale del Na^+ **v**oltaggio dipendente

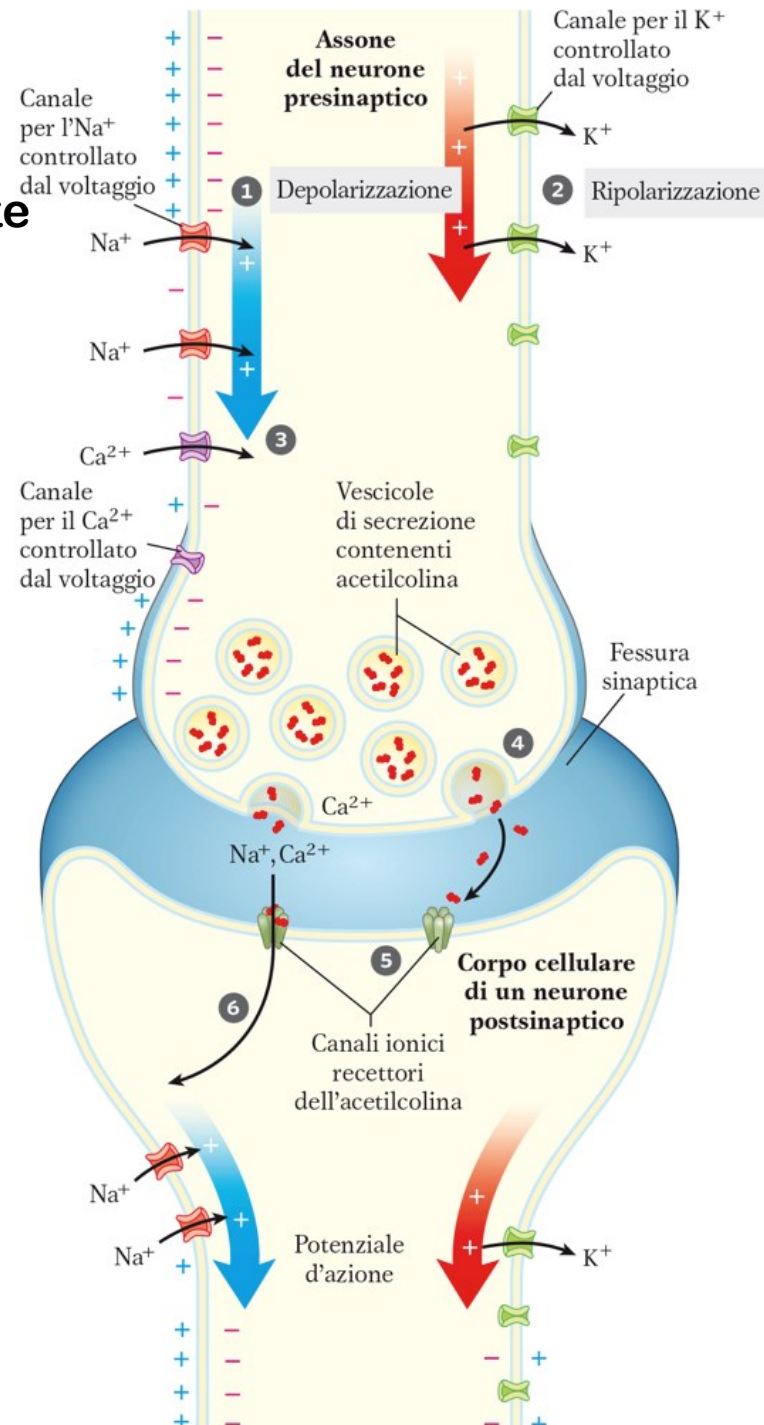


Canale del Na^+ voltaggio dipendente

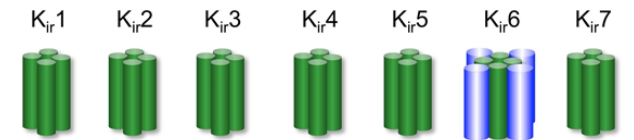
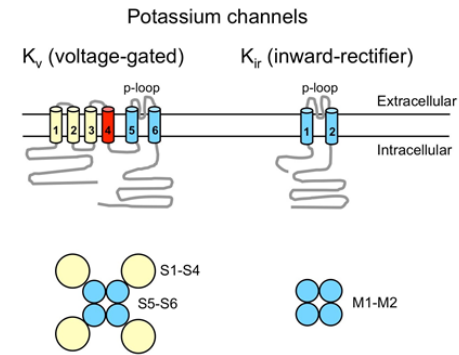


Si aprono quando la membrana si depolarizza localmente in risposta ad uno stimolo (neurotrasmettitore)

I canali per il Na^+ hanno un periodo refrattario che assicura la trasmissione unidirezionale dell'impulso elettrico



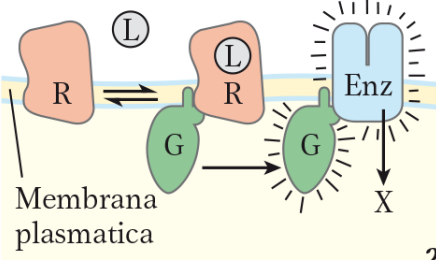
I canali K^+ si aprono una frazione di secondo dopo i canali per il Na^+ e contribuiscono a ripolarizzare la membrana



Principali tipi di recettori/trasduttori di segnale

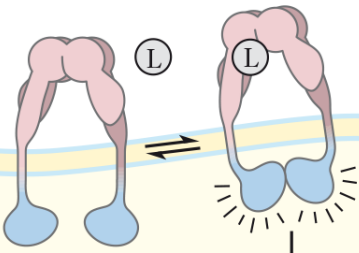
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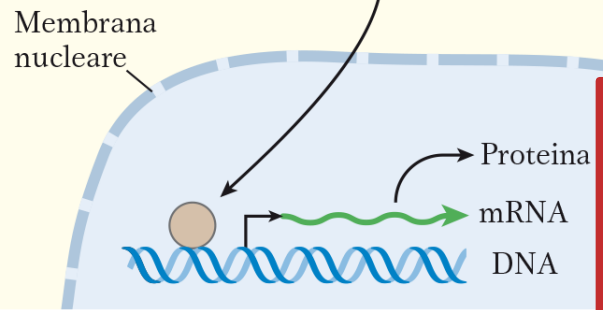


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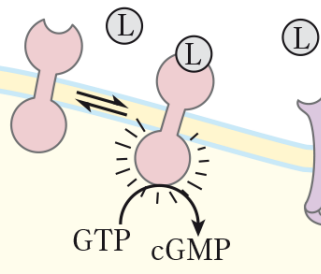


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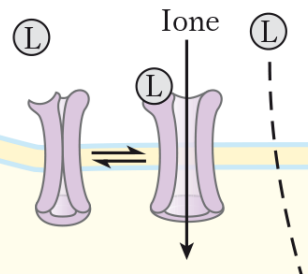
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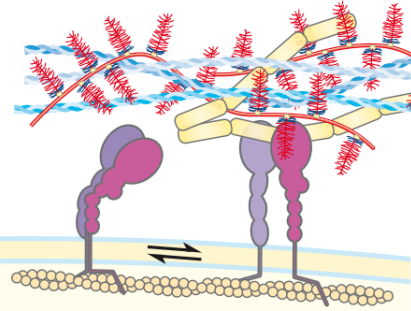
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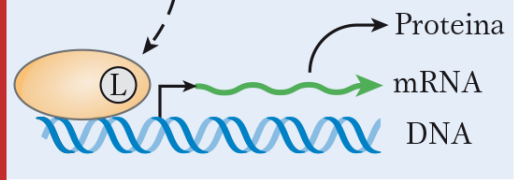
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6. Recettore nucleare

Il legame dell'ormone permette al recettore di regolare l'espressione di geni specifici.



GPCRs classification

based on
sequence homology

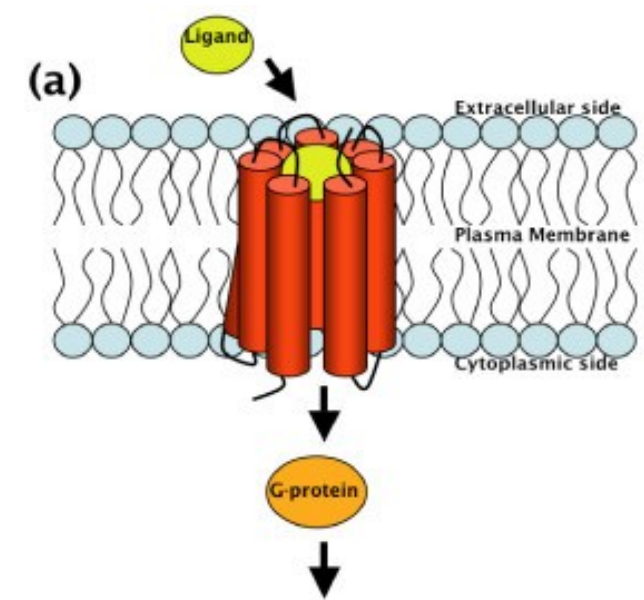
based on
phylogenetic origin

%	
85.5	Class A (or 1) Rhodopsin-like
7	Class B (or 2) Secretin-like
3.81	Class C (or 3) Metabotropic/Glutamate
0.45	Class D (or 4) Fungal mating receptors
0.38	Class E (or 5) Cyclic nucleotide receptors
2.84	Class F (or 6) Frizzled/smoothened

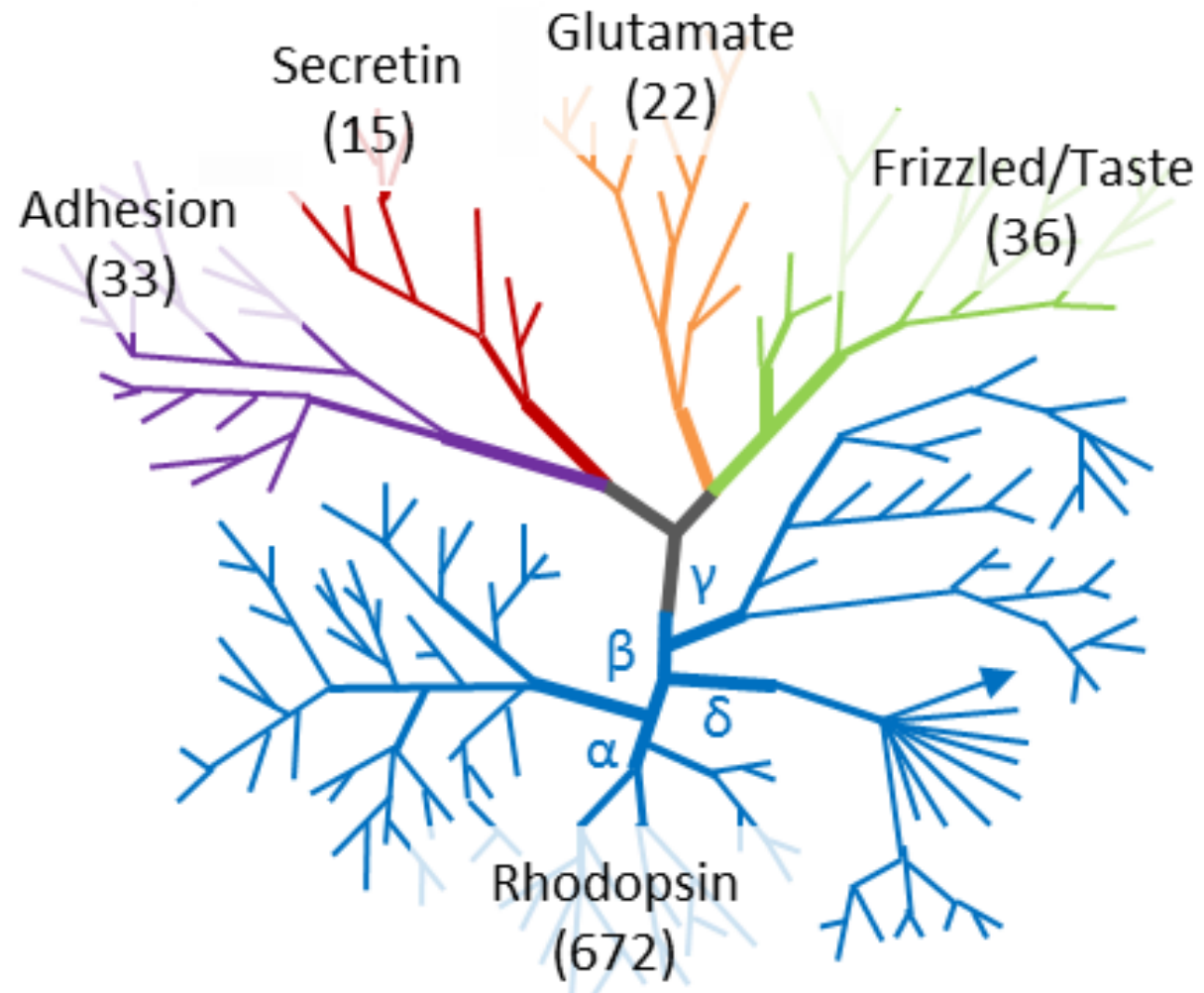
G
R
A
F
S

S
Y
S
T
E
M

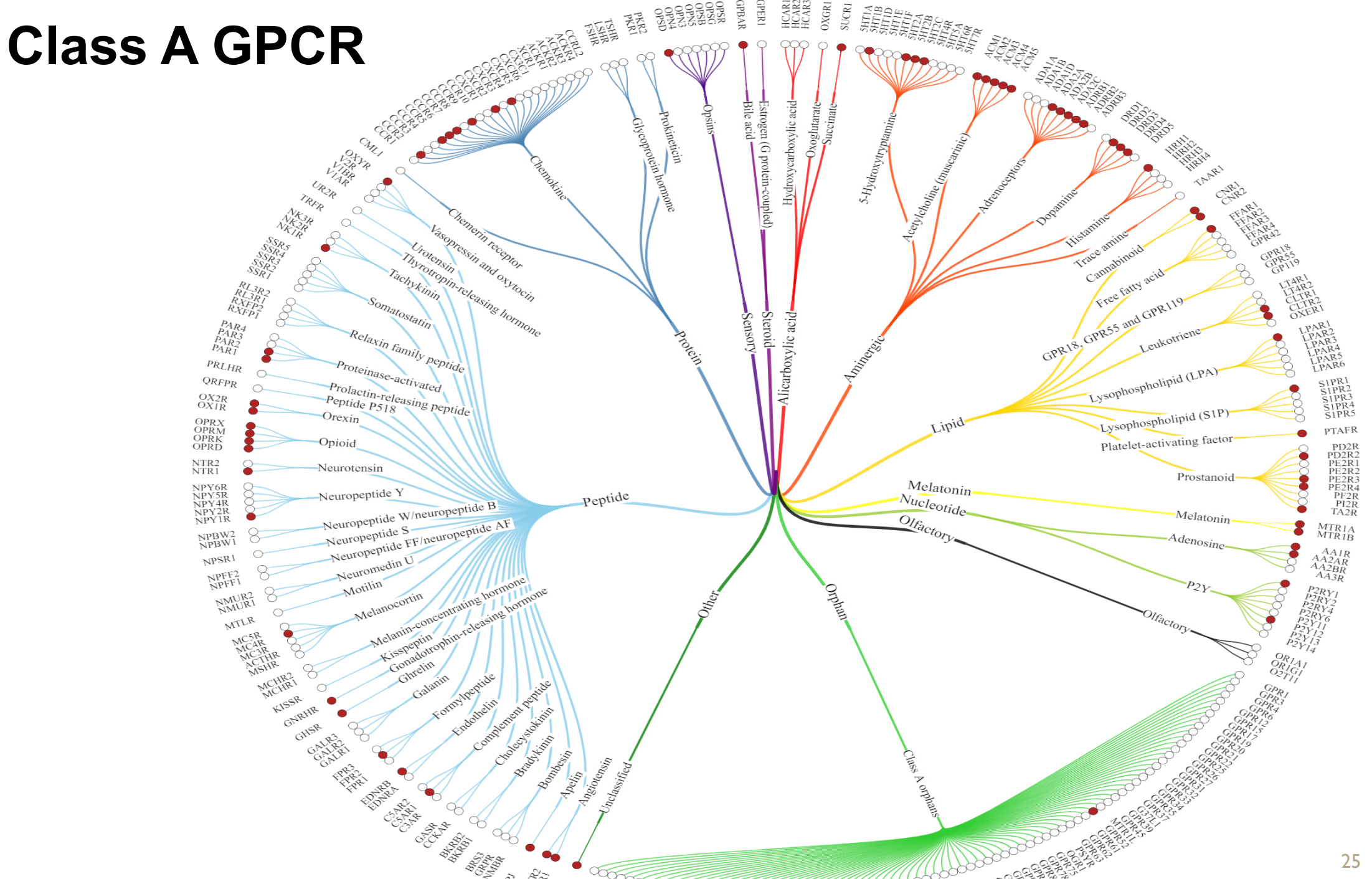
Glutamate (22 members)
Rhodopsin (701 members)
Adhesion (33 members)
Frizzled/Taste 2 (11 members)
Secretin (15 members)



La superfamiglia dei recettori accoppiati alle proteine G (GPCR)

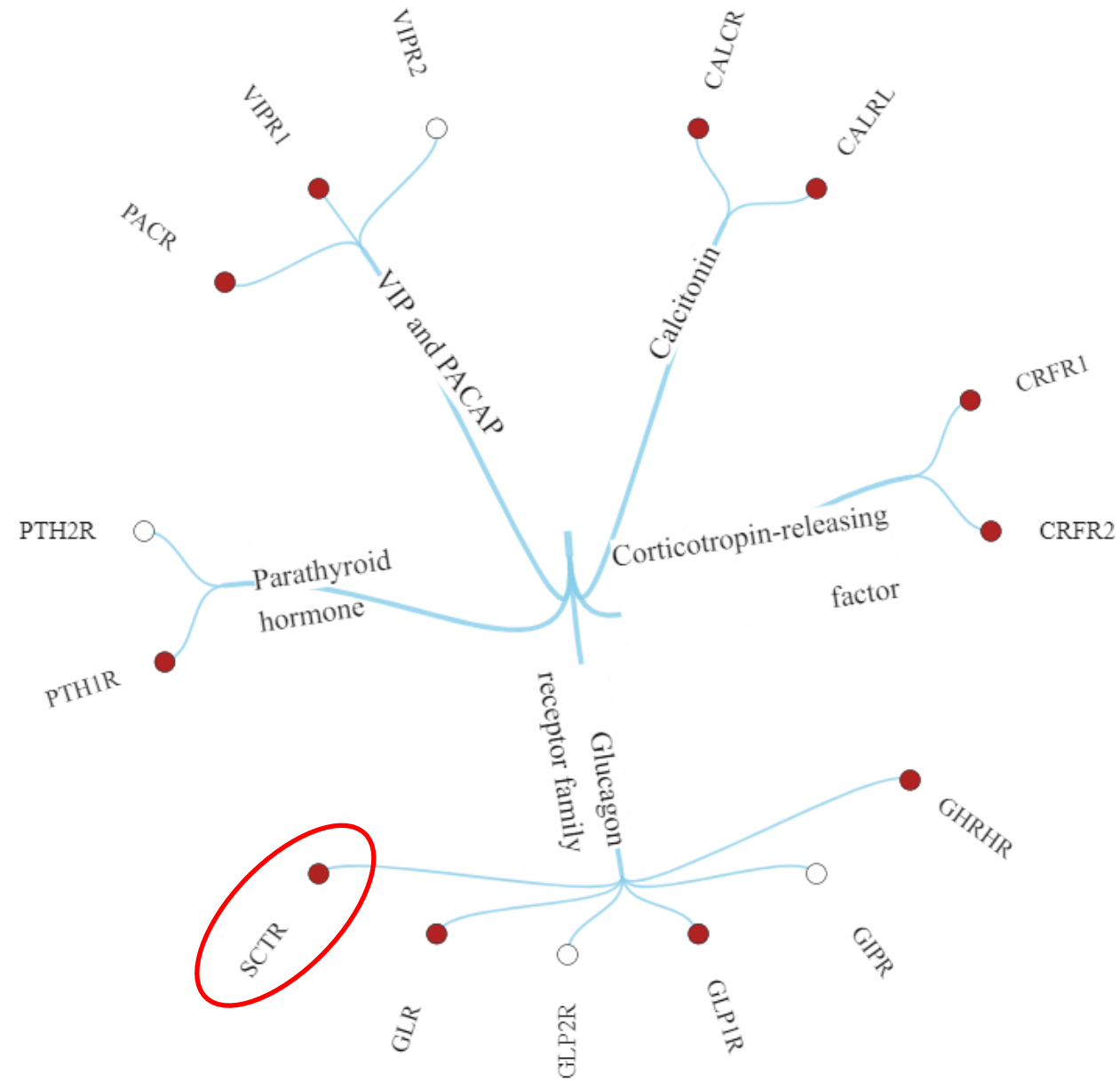


Class A GPCR

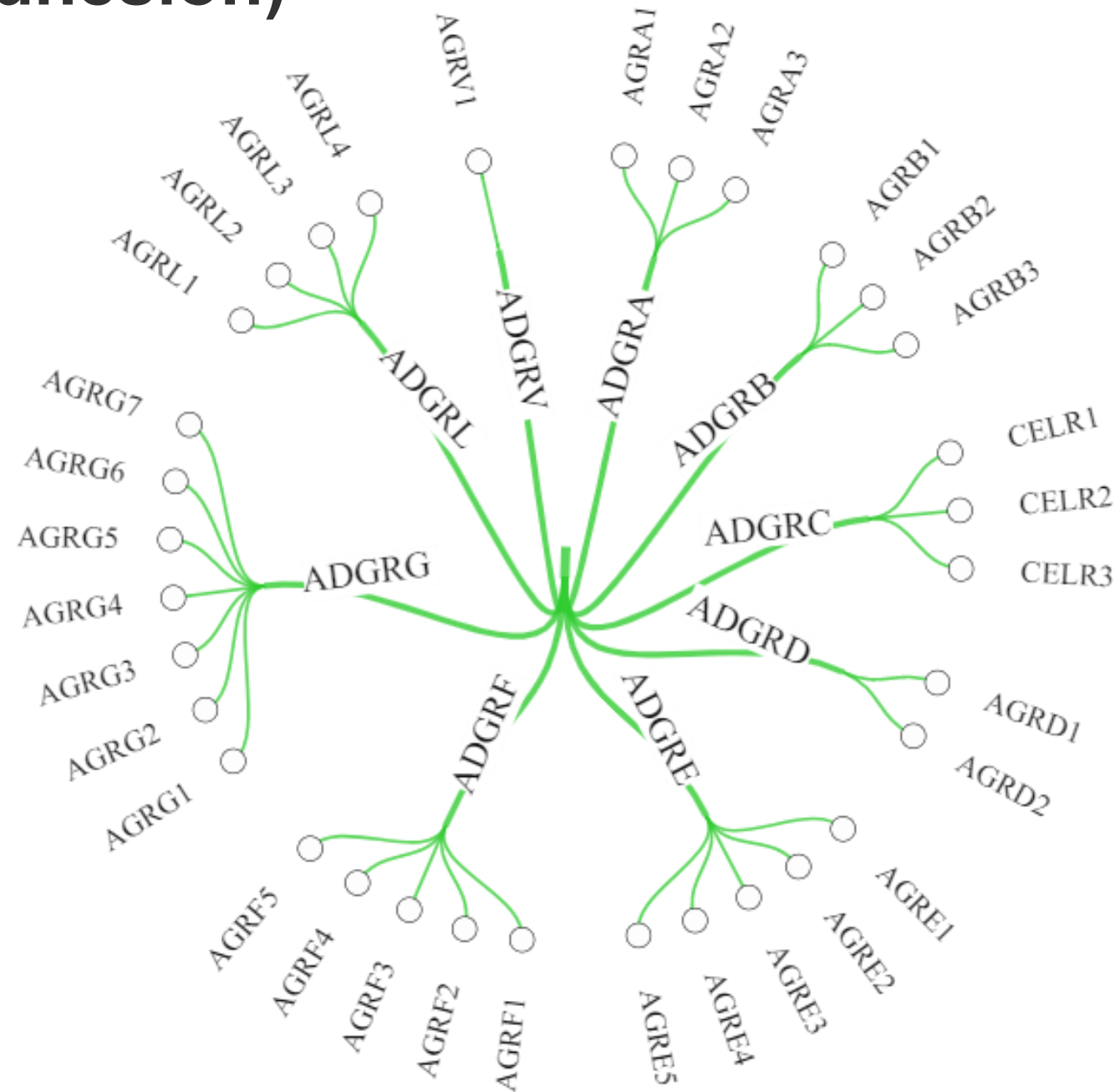


Class B1 (Secretin)

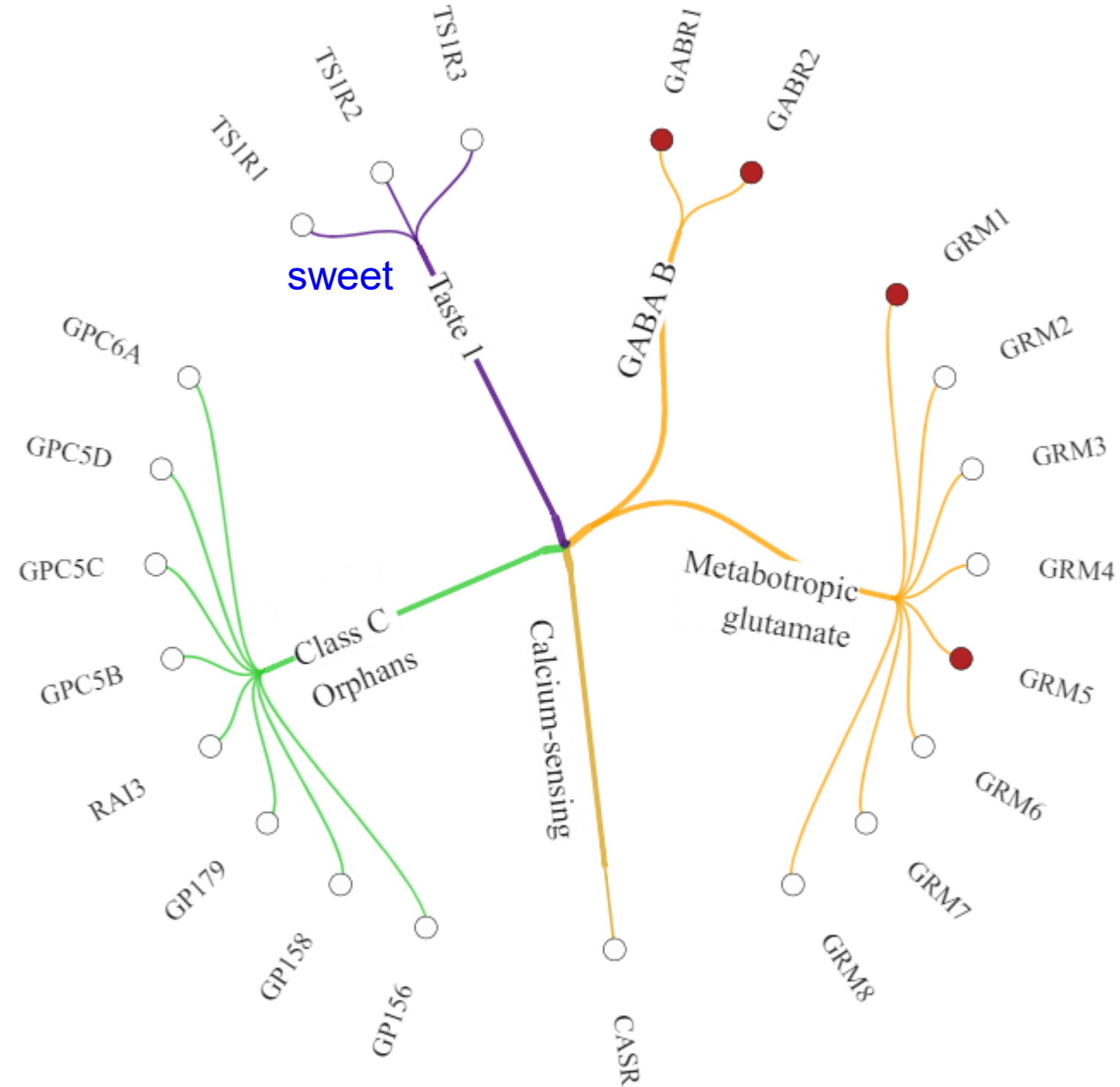
Ormone prodotto dal duodeno



Class B2 (Adhesion)

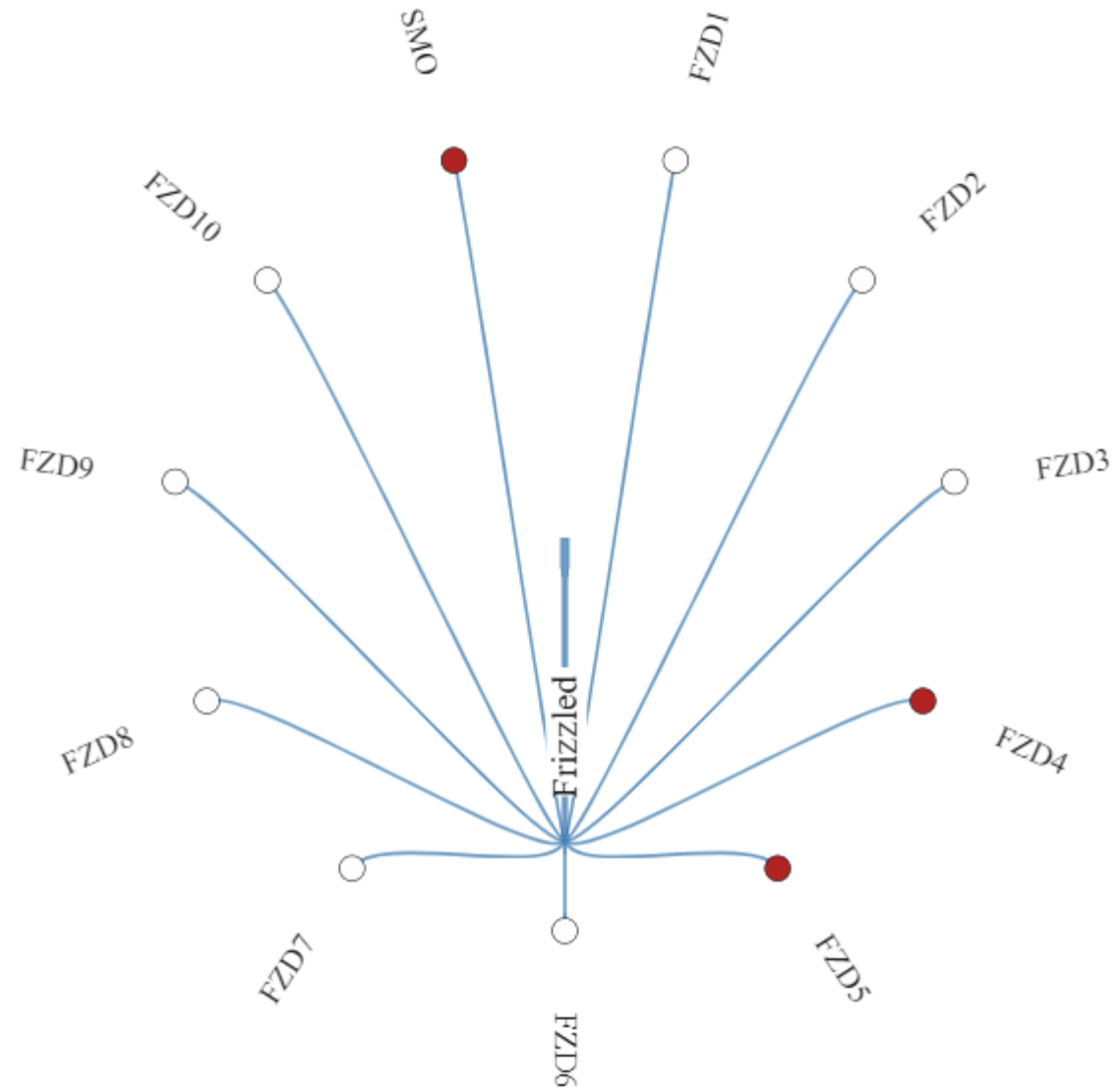


Class C (Glutamate)

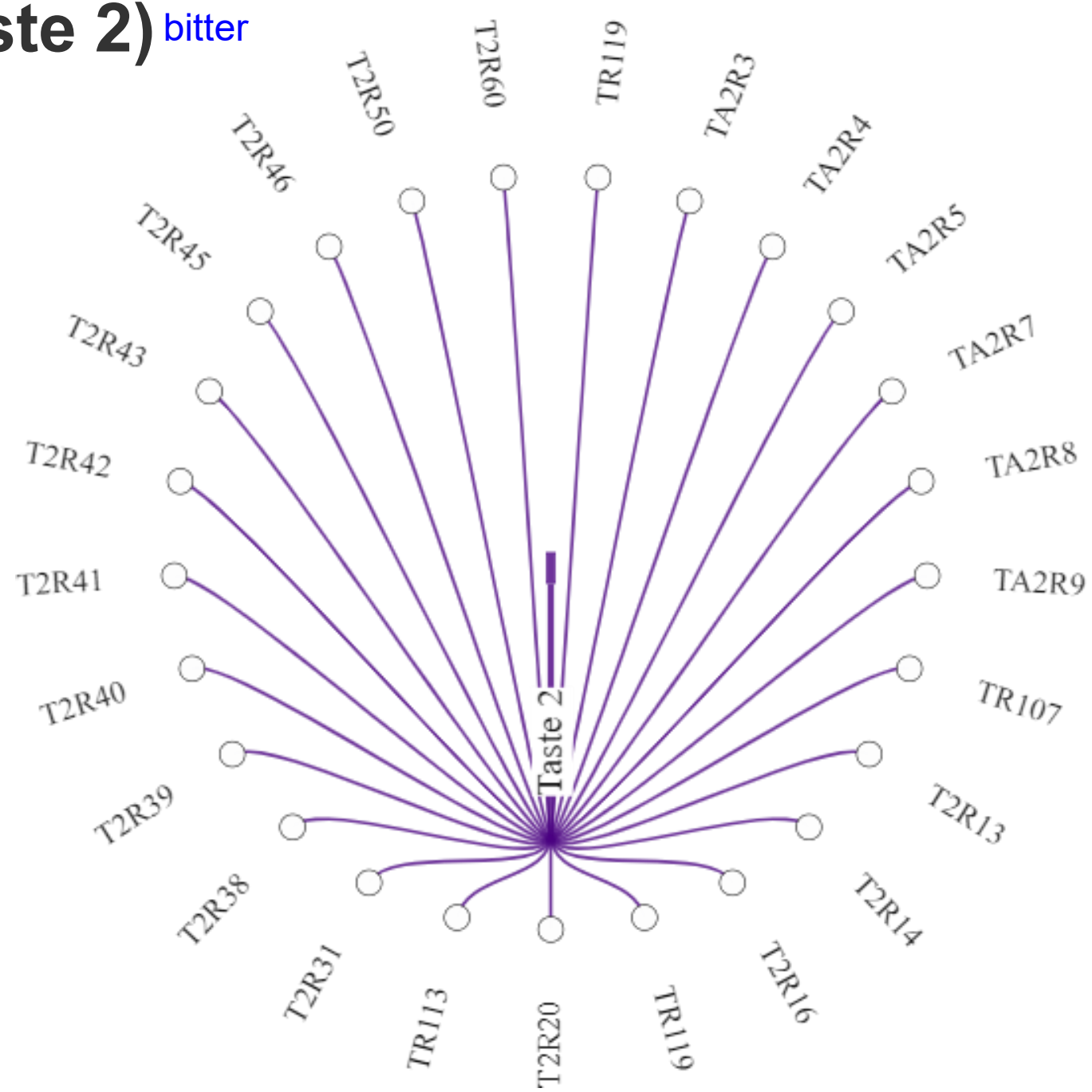


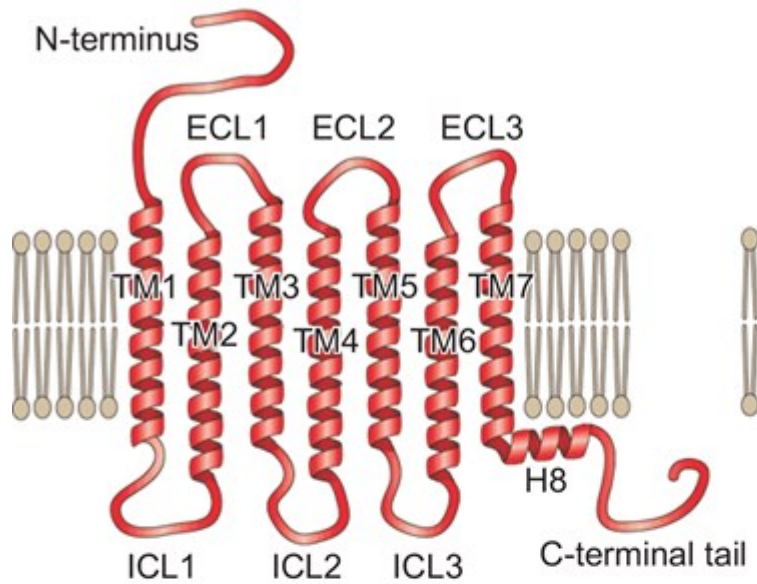
Class F (Frizzled)

Recettori per Wnt

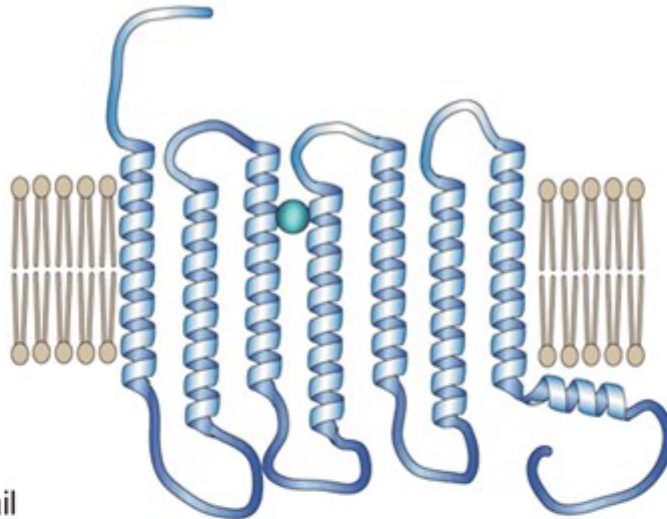


Class T (Taste 2) ^{bitter}

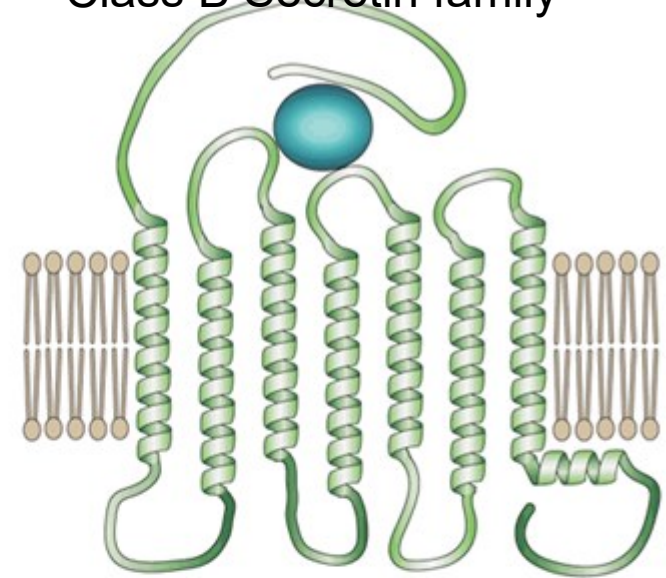




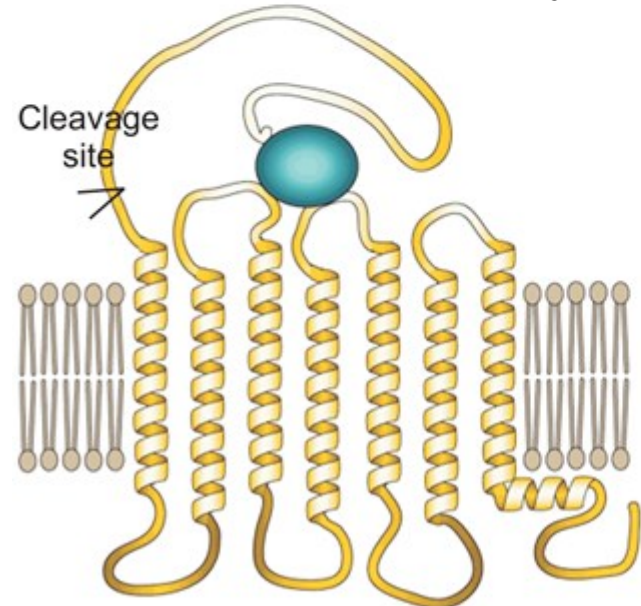
Class A Rhodopsin family



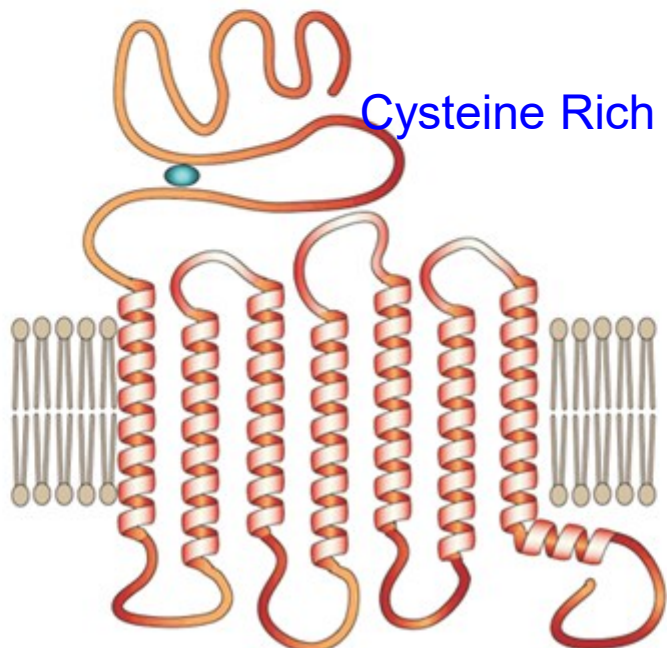
Class B Secretin family



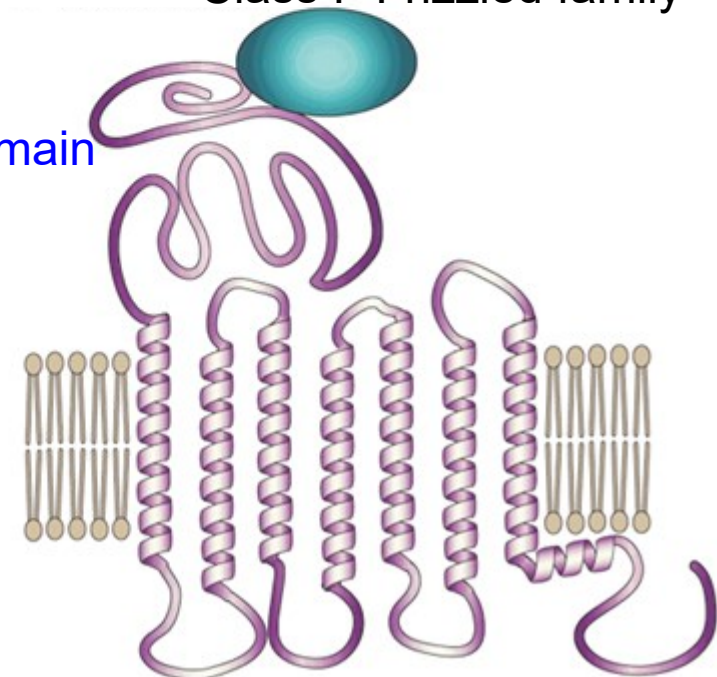
Class B Adhesion family



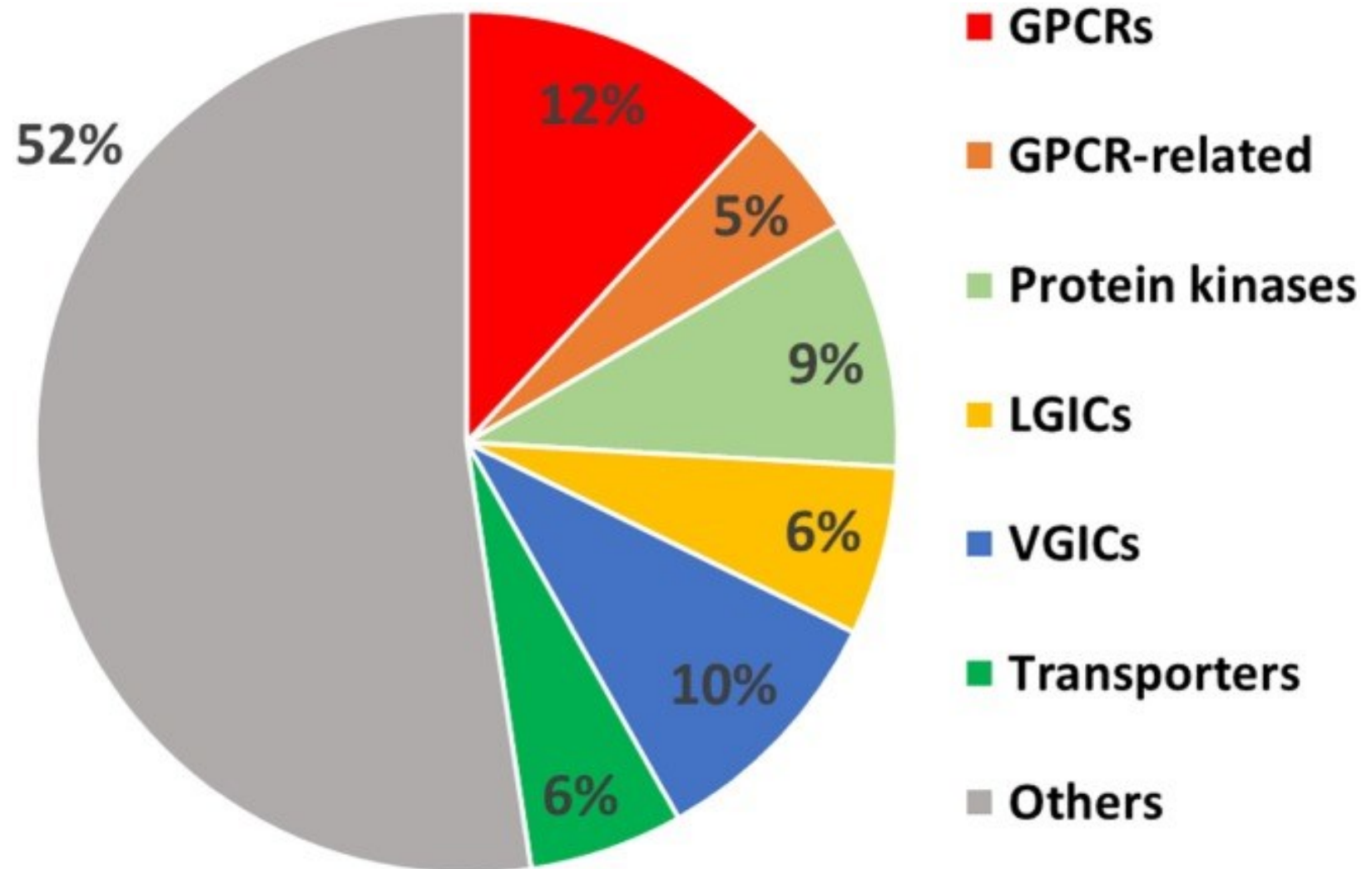
Class C Glutamate family



Class F Frizzled family



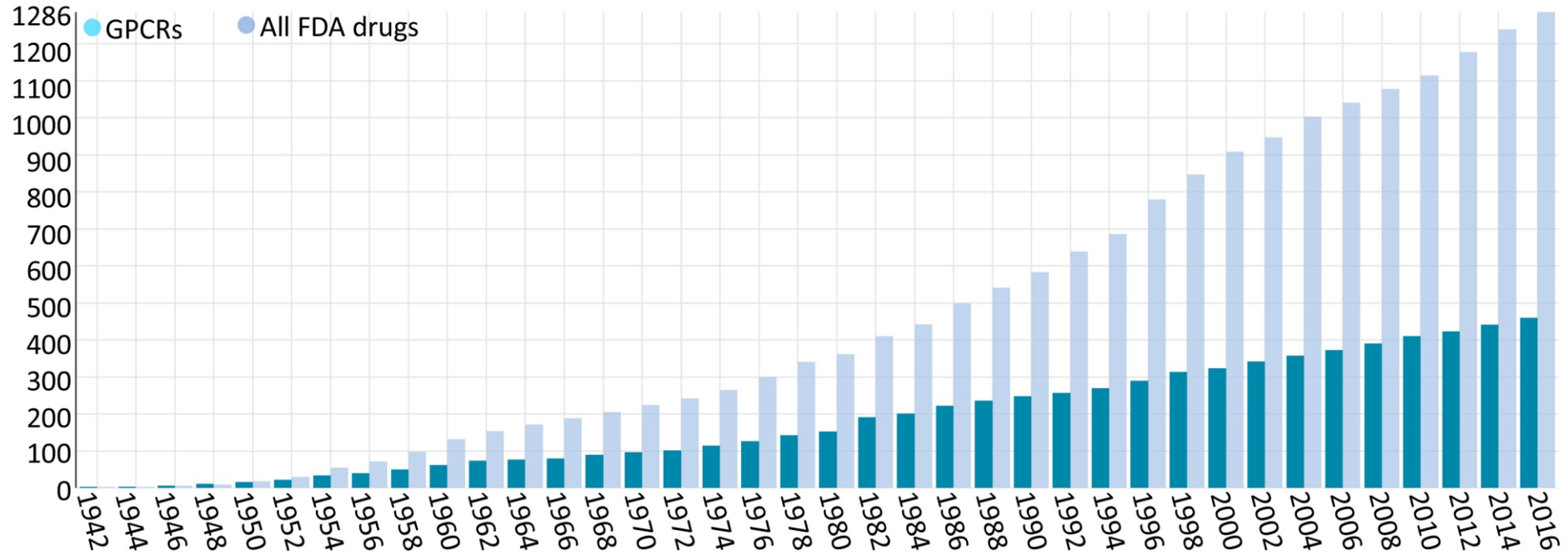
The estimated proportion of genes from different gene families that are targets for approved drugs.



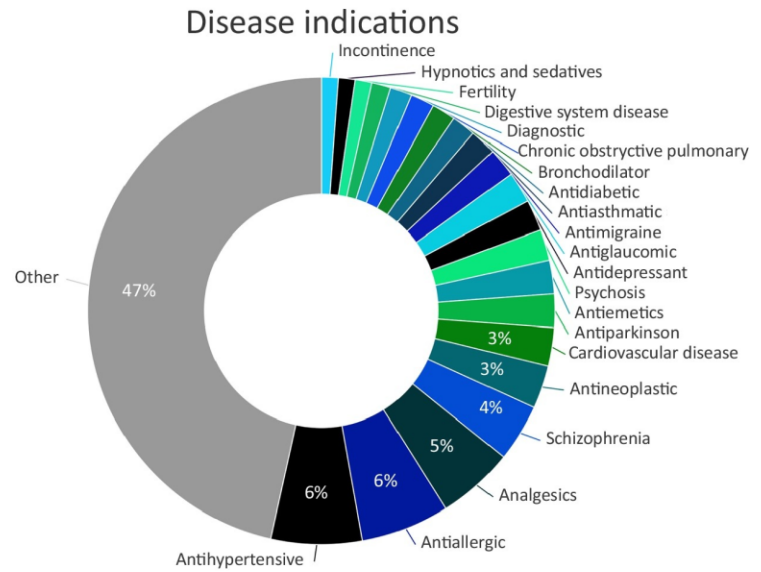
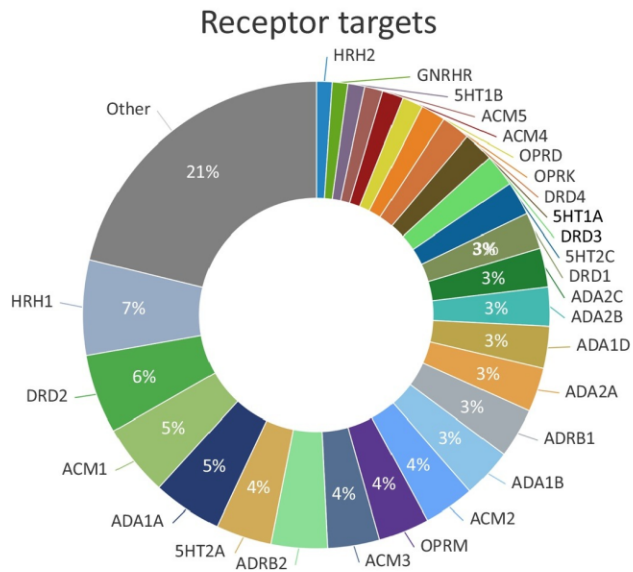
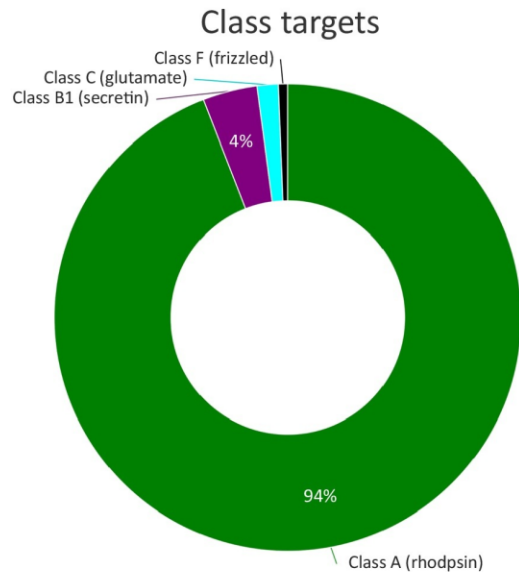
~1100 human gene/protein targets for approved drugs

There are 1286 drugs approved by the FDA, of which 460 drugs (36%) target GPCRs

(A)

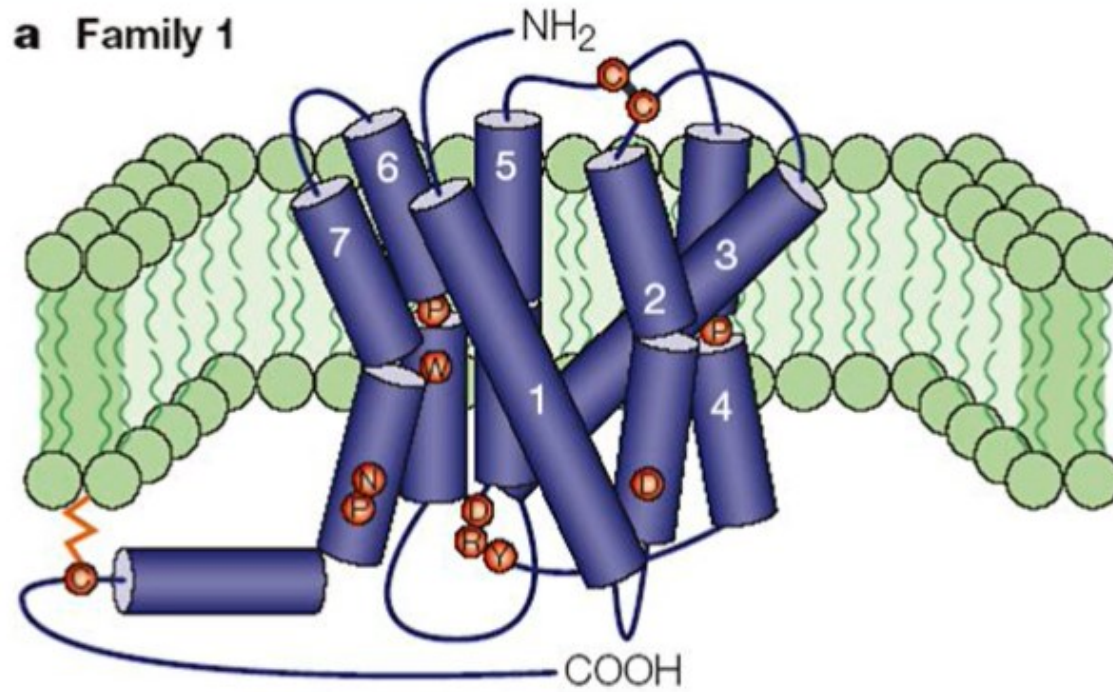


(B)



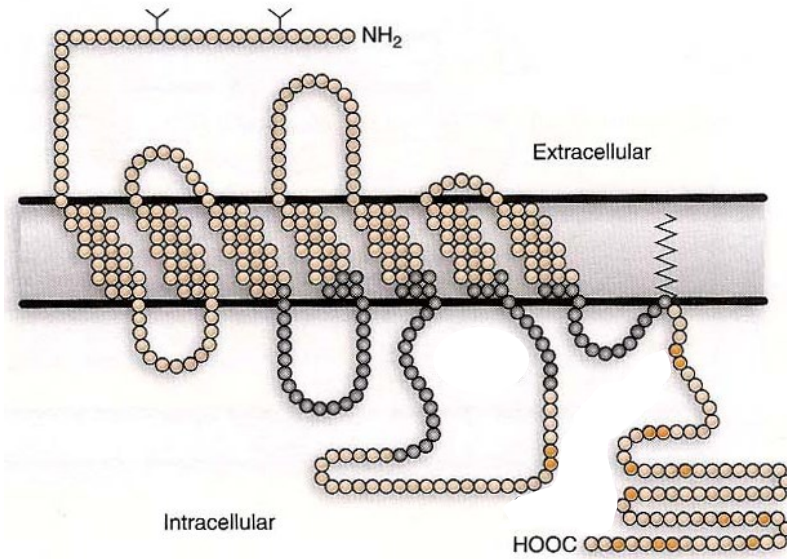
GPCR signalling cascades

a Family 1



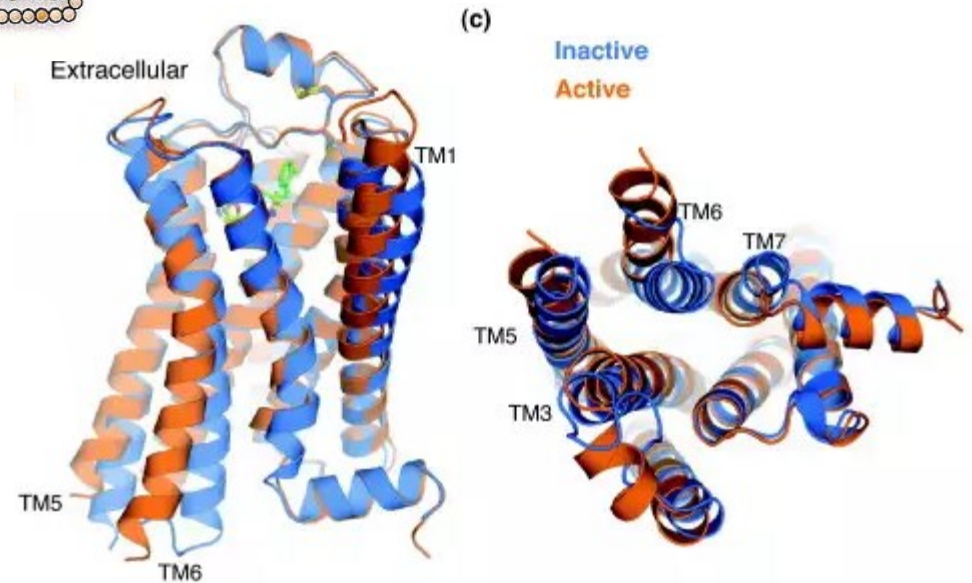
- ❖ Represent the predominant class of GPCRs;
- ❖ Several highly conserved amino acid (red circles);
- ❖ Disulfide bridge between first and second extracellular loops (ECLs), palmitoylated cys in C-tail;
- ❖ The binding of small molecule ligands occurs within the TM region;
- ❖ Example: Rhodopsin, Dopamine receptor, Chemokine receptors;

β 2-Adrenergic receptor

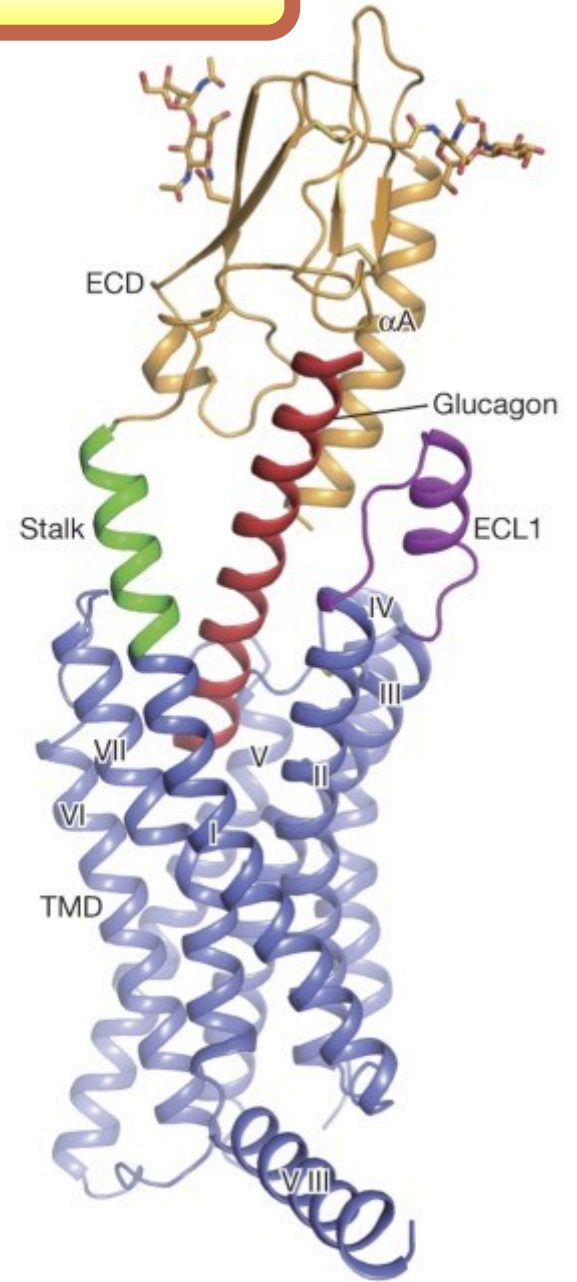
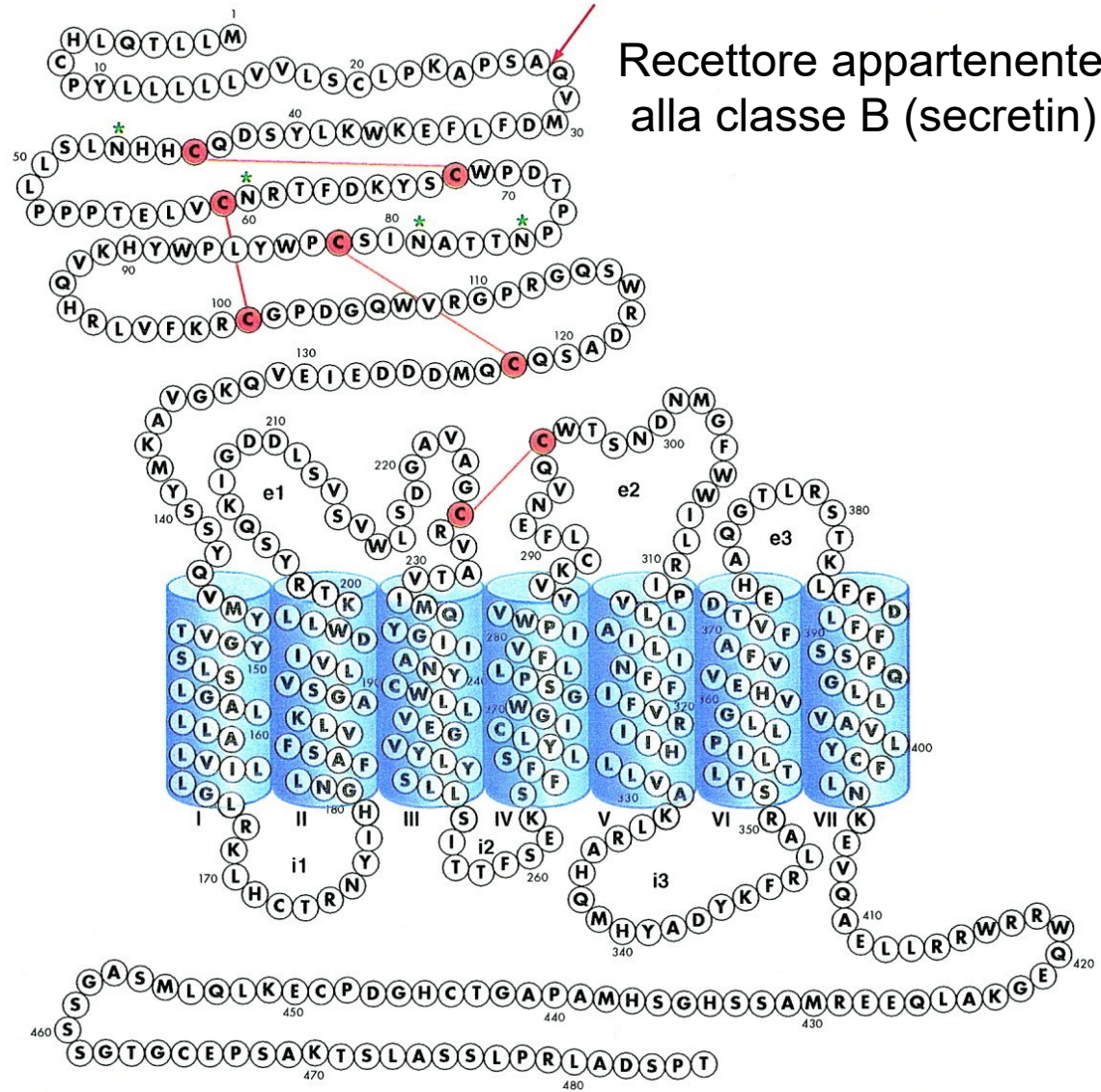


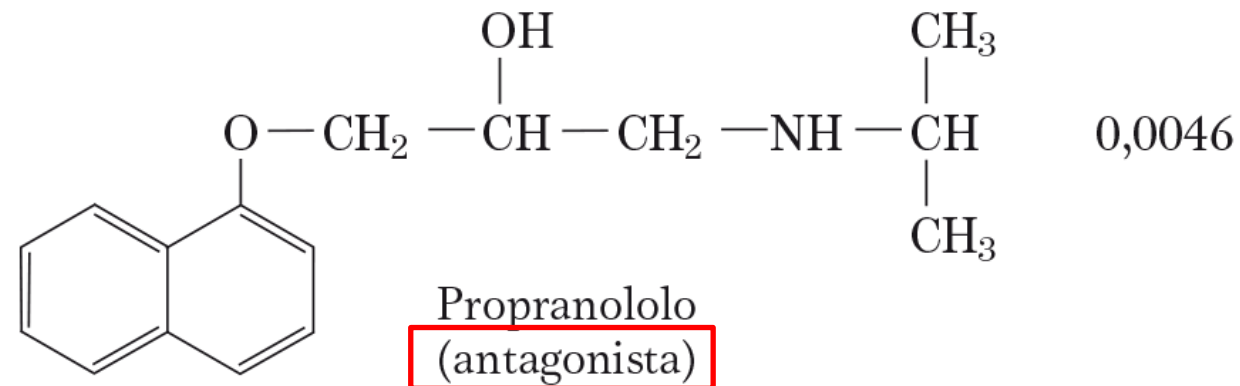
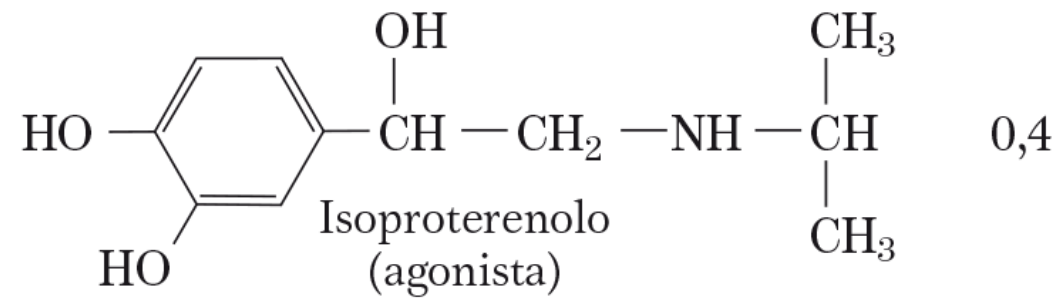
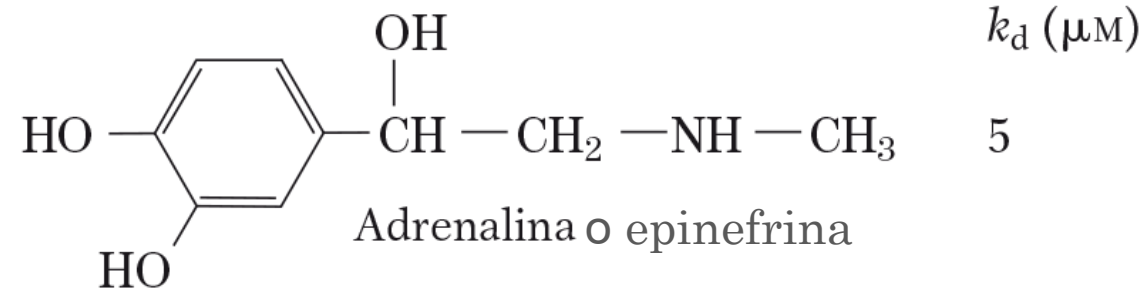
Membrana plasmatica

413 amminoacidi

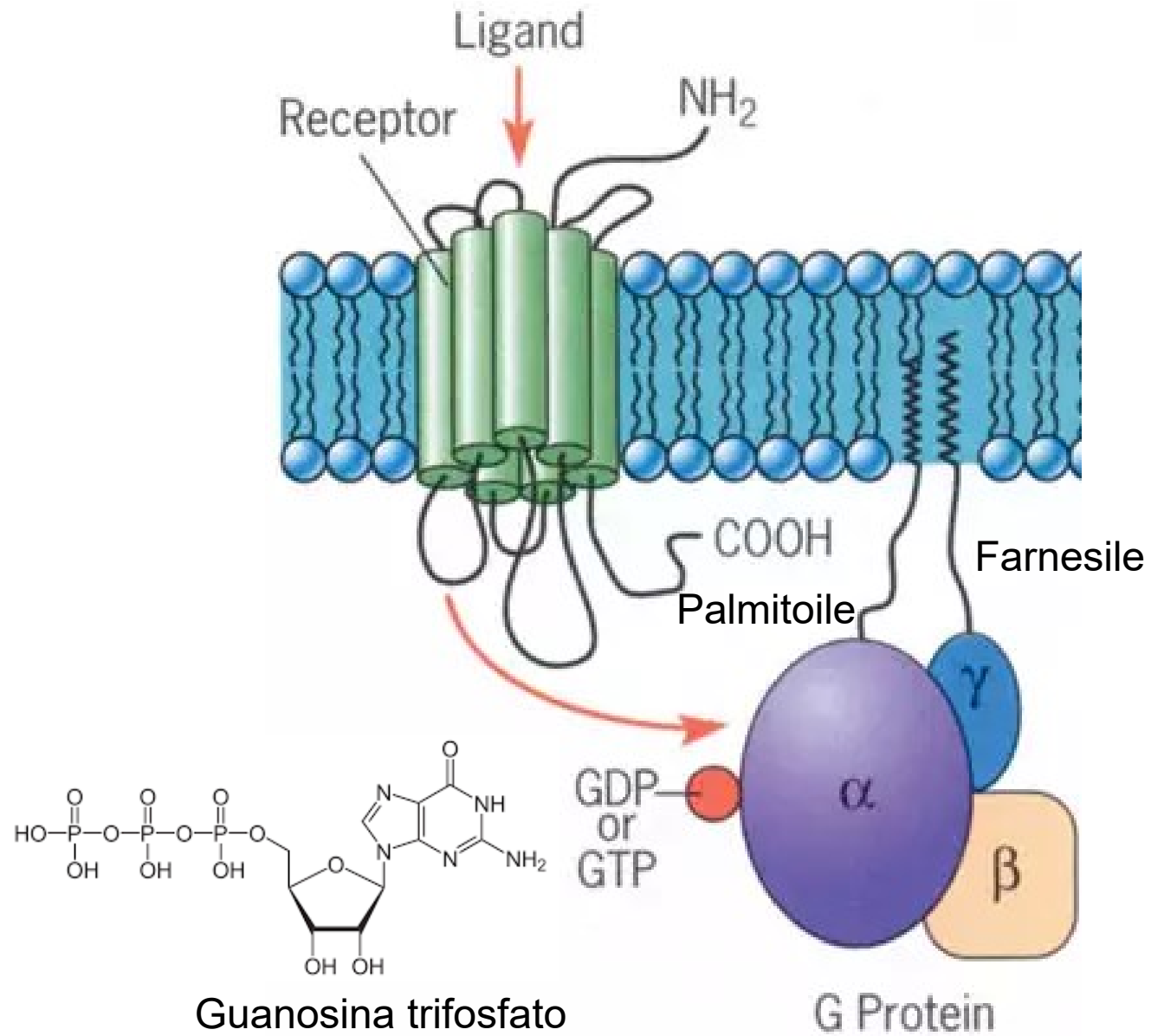


Recettore per il glucagone

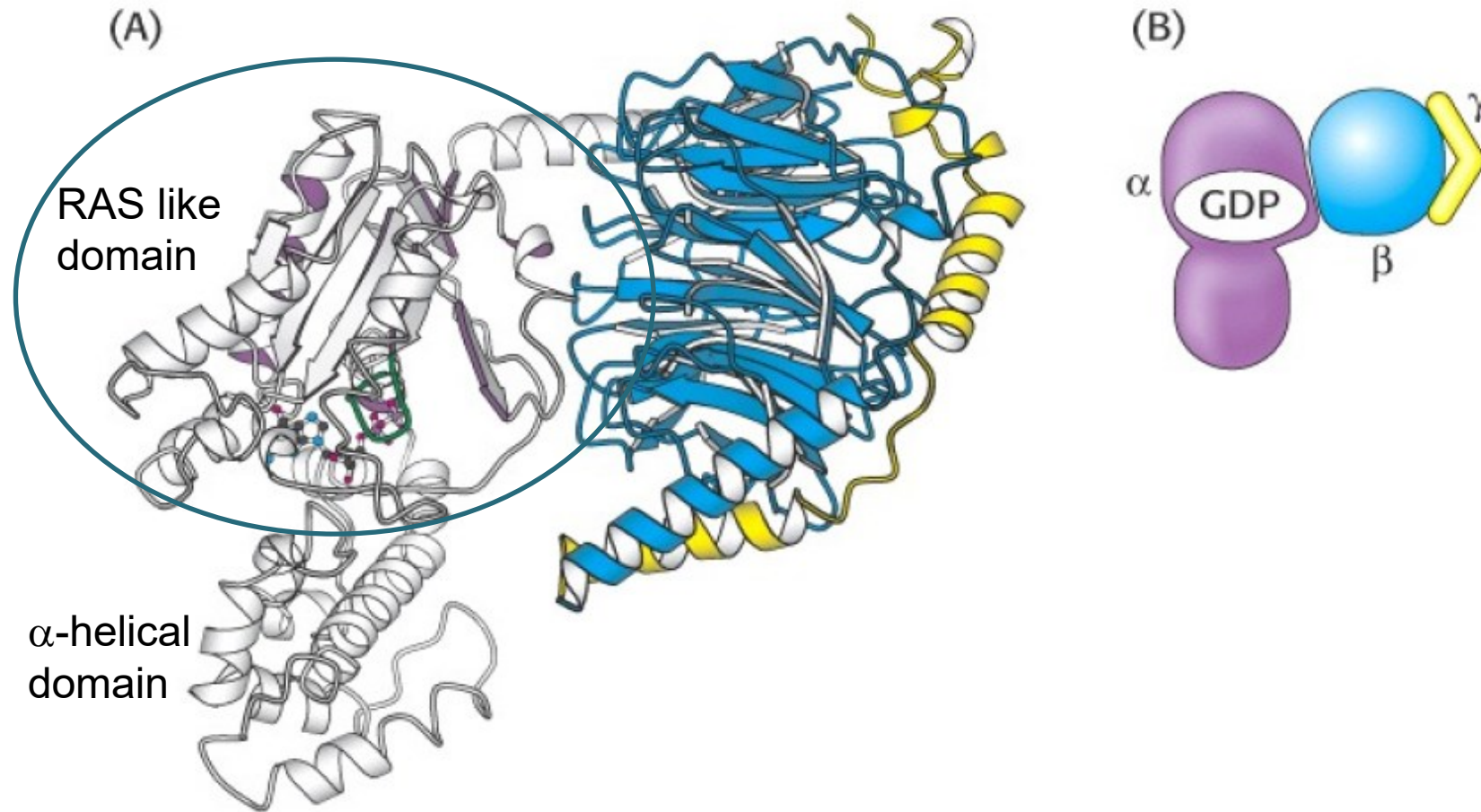




Trasduzione del segnale β AR

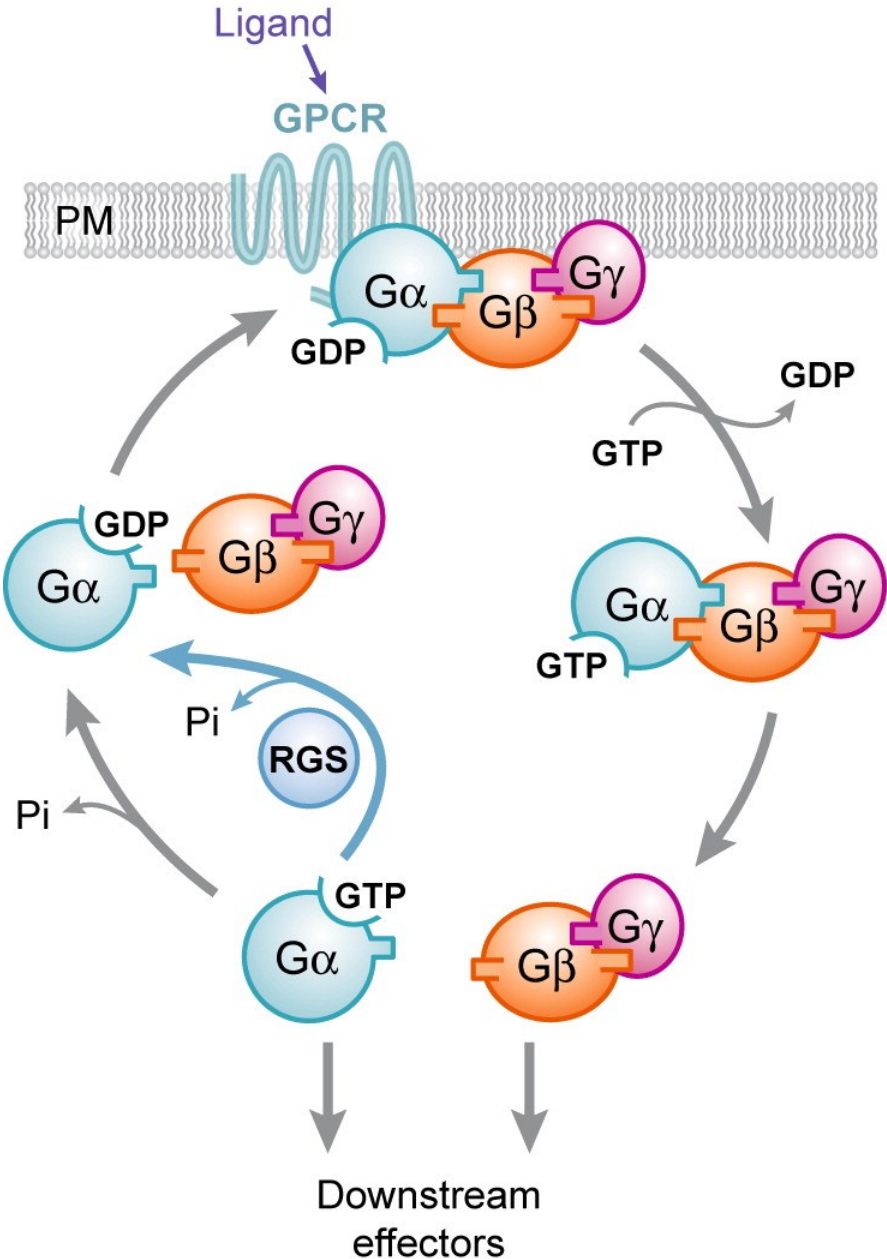


Struttura della proteina G

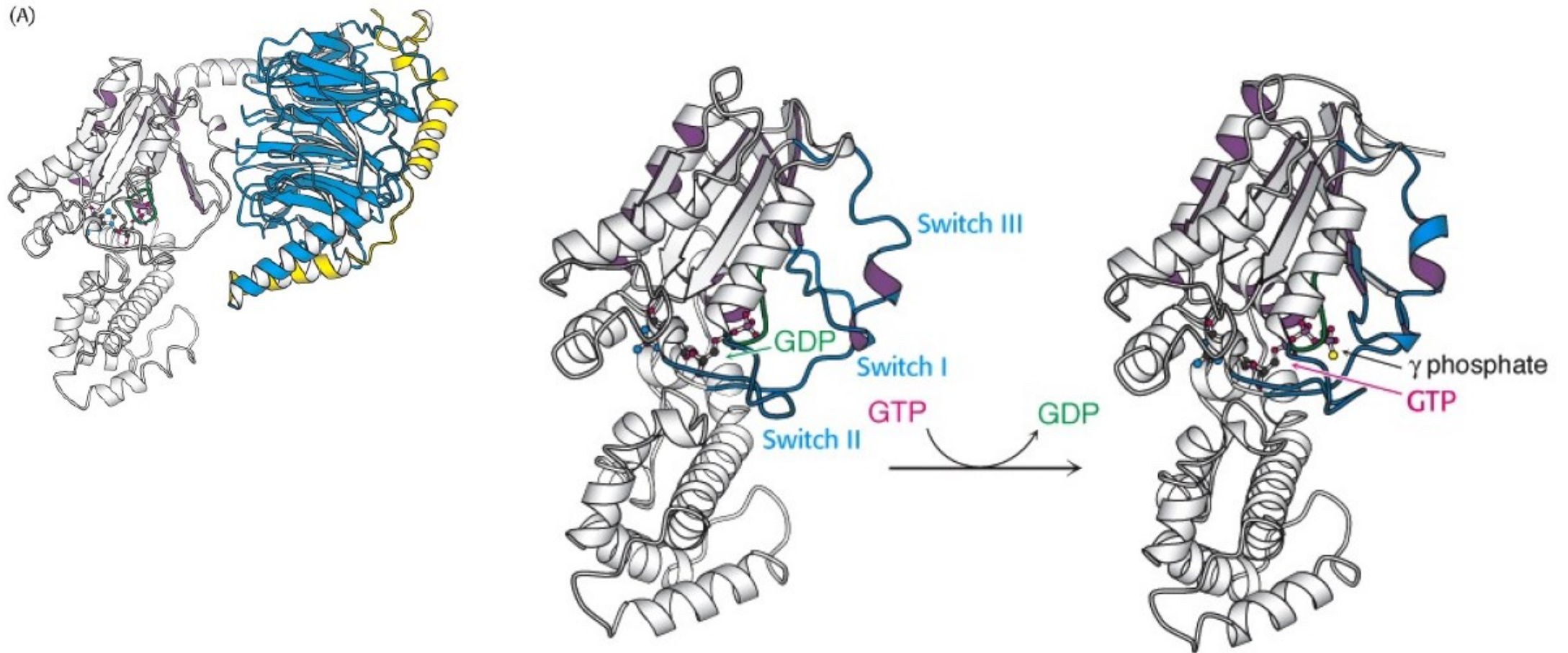


Le proteine G accoppiate ai recettori metabotropici sono **trimeri**, formati dalle subunità α (21 isoforme), β (6 isoforme) e γ (12 isoforme).

G protein cycle



Regioni della proteina G modificate durante l'attivazione/inattivazione

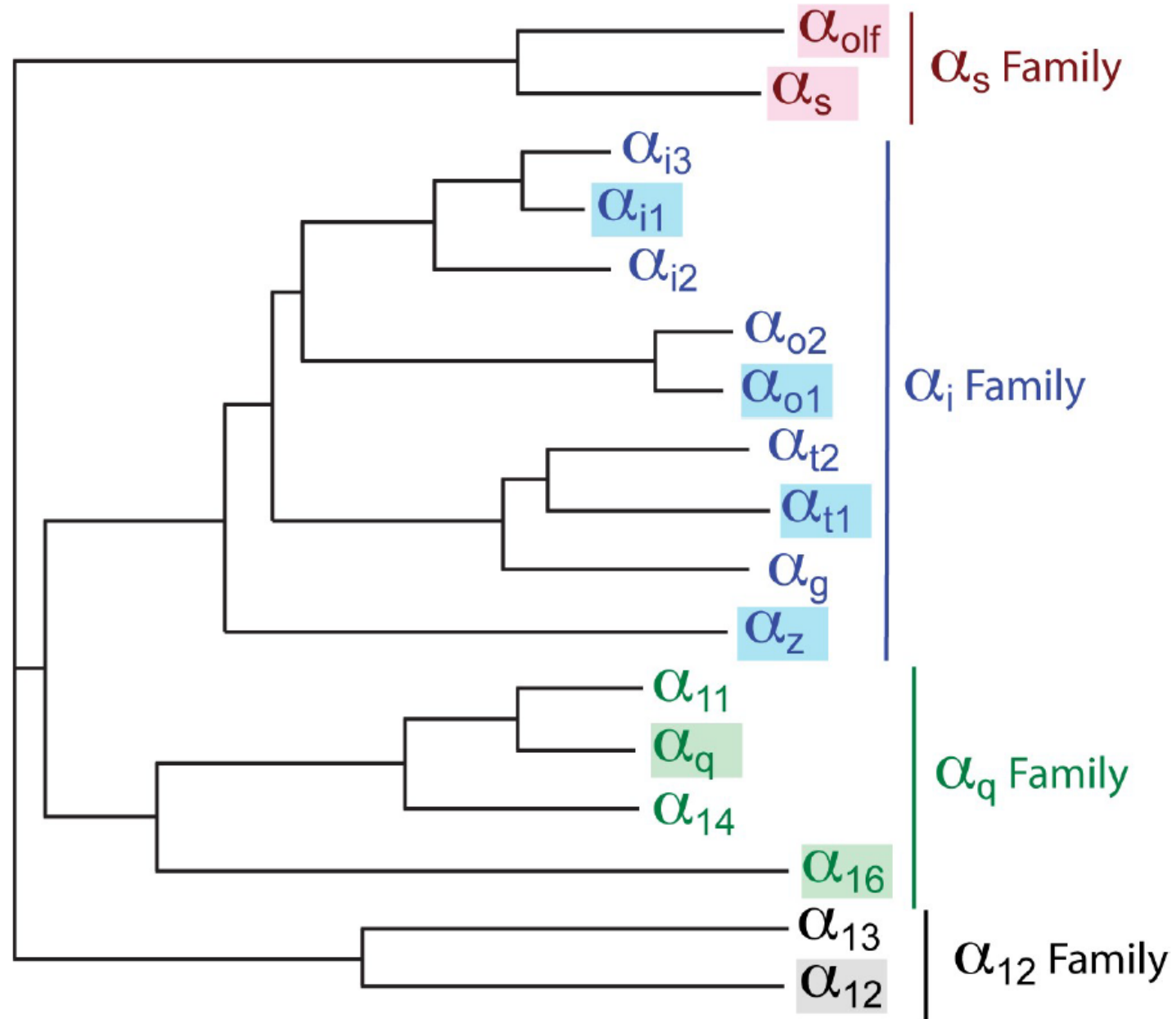


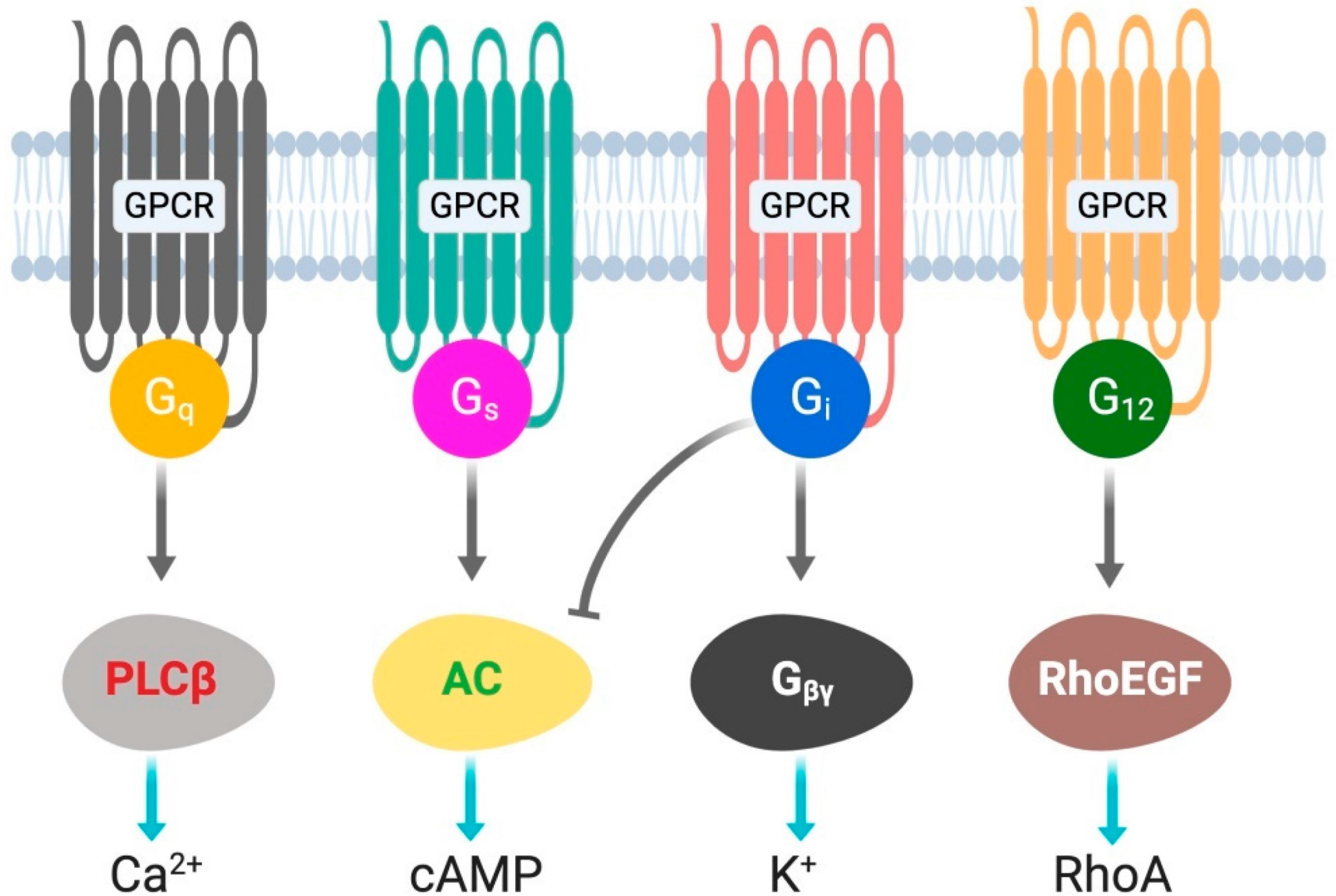
L'attivazione della proteina G consiste nella sostituzione di GDP con GTP che porta alla dissociazione del dimero $\beta\gamma$ dalla subunità α -GTP.

Trimeric G-proteins

SUBUNIT	SUB-TYPES	EXPRESSION (CELLS)	PRIMARY EFFECT	OTHER EFFECTS	RECEPTORS	TOXIN
G_s - family						
→ α_s - generic form	4	ubiquitous, including neurons	↑ AC (subtypes 1-10)	↑ cardiac Ca ²⁺ channels ↑ K _{Ca} channels ↓ Na ⁺ channels	NE, EPI, histamine, LH, FSH	CTX
α_{olf}	1	olfactory epithelium; some neuronal ganglia	↑ AC (subtypes 1-6)		odorant chemicals	CTX
G_i - family						
α_o	≥ 2	neurons; neuroendocrine cells; astroglia; cardiac muscle	↑ PLC-β	↓ AC ↓ L- & N-type Ca ²⁺ channels ↑ neuronal K ⁺ channels	ACh, NE, opiates, All, many peptides	PTX
α_i	13	ubiquitous, including neurons	↓ AC (subtypes 1-10)	↑ K _{ATP} channels ↑ K _v channels ↓ L- & N-type Ca ²⁺ channels	same as above	PTX
α_z	≥ 1	platelets; adrenals	↓ AC	↑ PLC	same as above	none
G_q - family						
→ α_q	≥ 5	ubiquitous	↑ PLC-β		ACh, NE	none
$\alpha_{11,14}$?	ubiquitous	↑ PLC-β		ACh, NE	none
Unrelated?						
α_t (transducin)	≥ 2	outer segments of retinal rods & cones	↑ γ PDE (cGMP-PDE)		light	CTX, PTX
α_{gust} (gustducin)	≥ 2	taste bud receptors	↑ PLC-β	↑ cAMP-PDE	chemical stimuli	CTX, PTX
$\alpha_{12,13}$	≥ 2	ubiquitous	↑ GTPases	↑ nucleotide exchange	mechanical stimuli	?

Phylogenetic relationship of human $G\alpha$ subunits

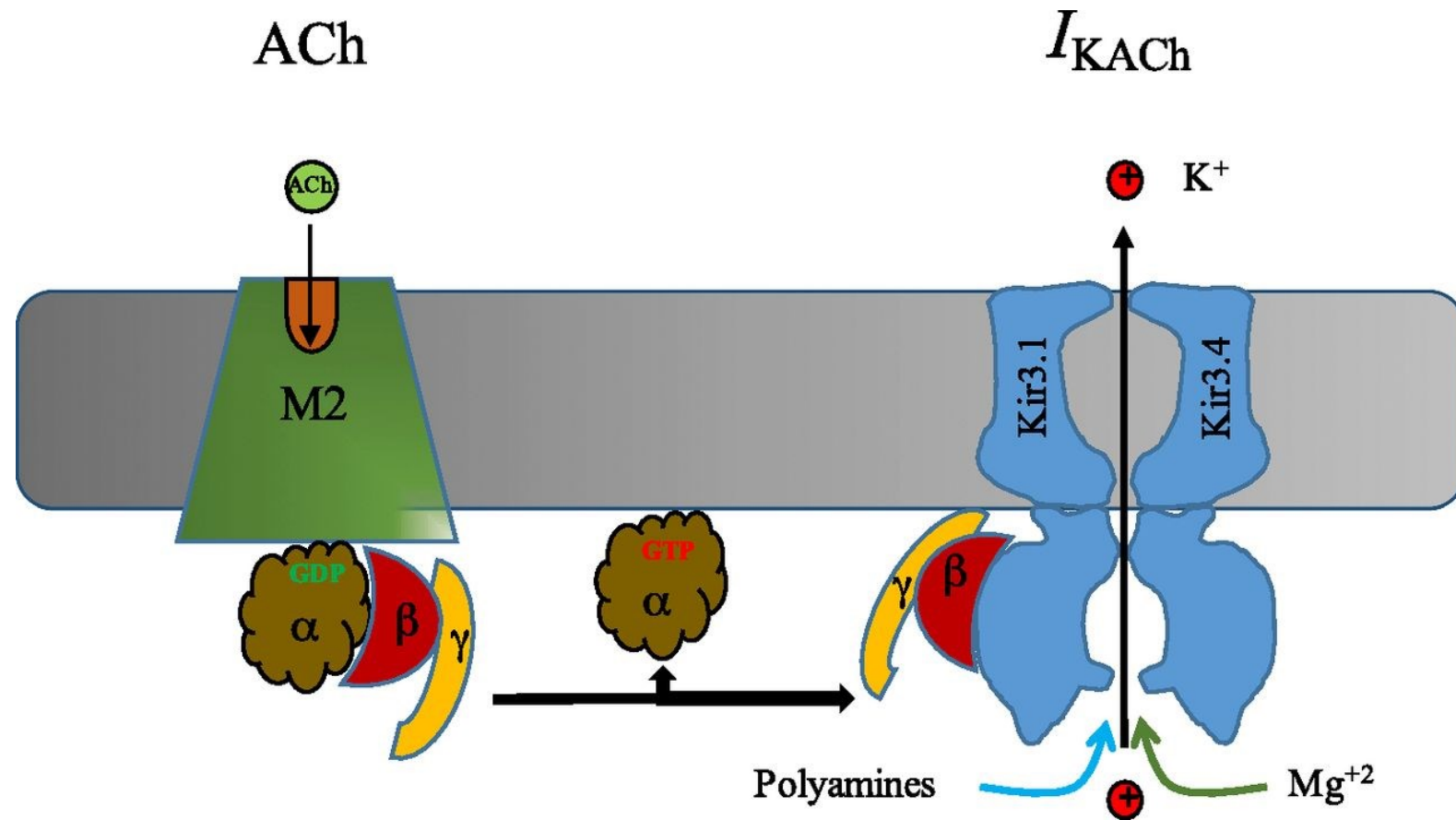




$\beta\gamma$ effectors

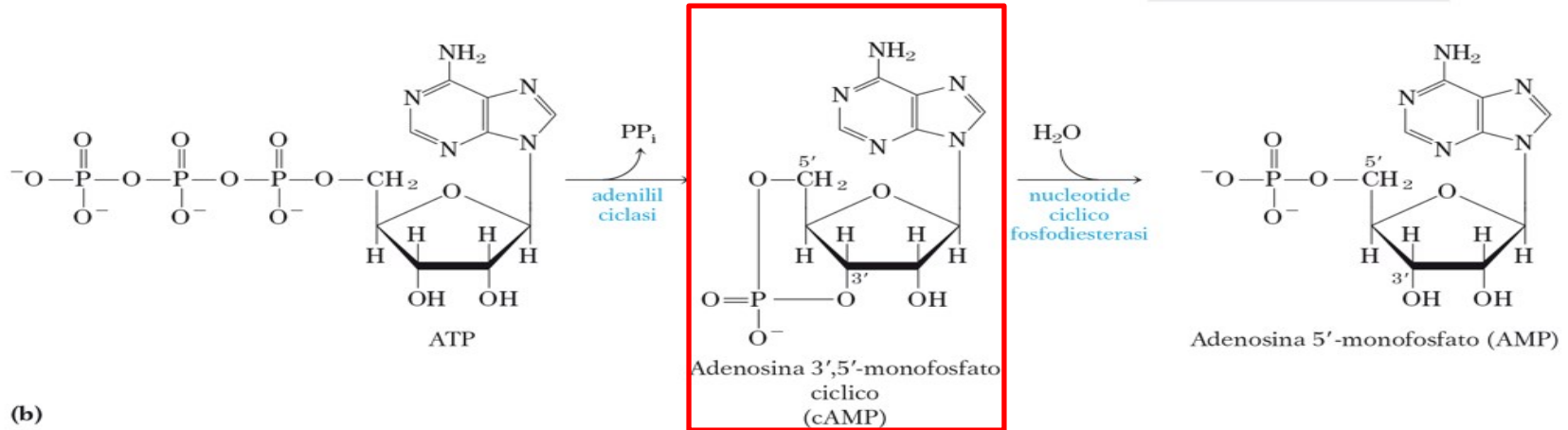
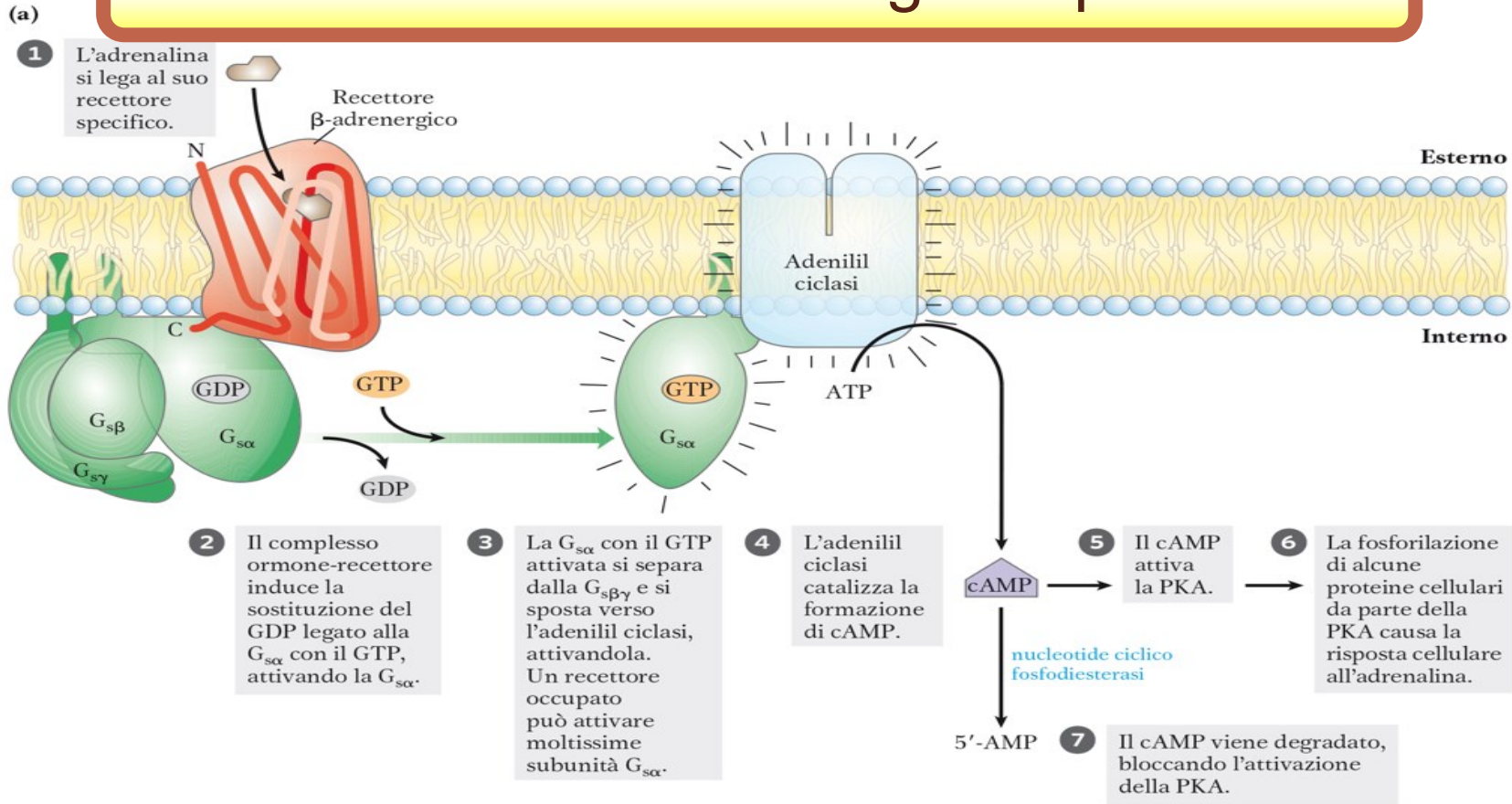
	Effector	Signalling effect
→	<u>GIRK2</u>	activation
	<u>GIRK4</u>	activation
	<u>N-type calcium channel</u>	inhibition
	<u>P/Q-type calcium channels</u>	inhibition
	<u>Phospholipase A</u>	activation
→	<u>PLCβ1</u>	activation
	<u>PLCβ2</u>	activation
	<u>PLCβ3</u>	activation
→	<u>Adenylyl cyclase</u> Type I, III, V, VI, VII	inhibition
	Adenylyl cyclase Type II, IV	activation
	<u>PI3K</u>	inhibition
→	<u>βARK1</u>	activation
	<u>βARK2</u>	activation
	<u>Raf-1</u>	activation
	<u>Ras exchange factor</u>	activation
	<u>Bruton's tyrosine kinase</u>	activation

Parasympathetic signaling pathway in cardiac cells

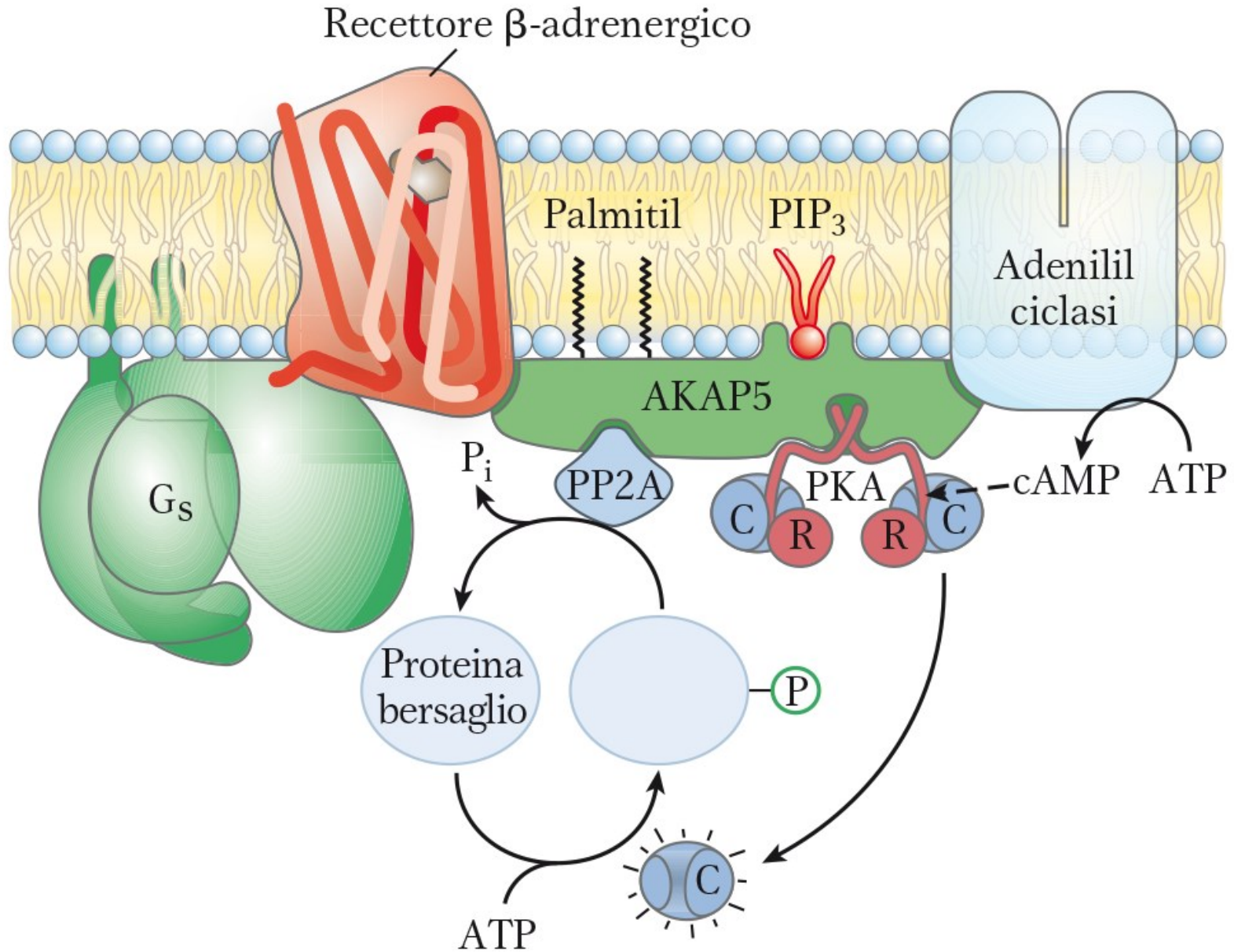


The binding of ACh to M2R induces dissociation of the $\beta\gamma$ -complex (from Gi/o proteins) to directly interact with the K_{ACH} channel and then decreases cardiac excitability.

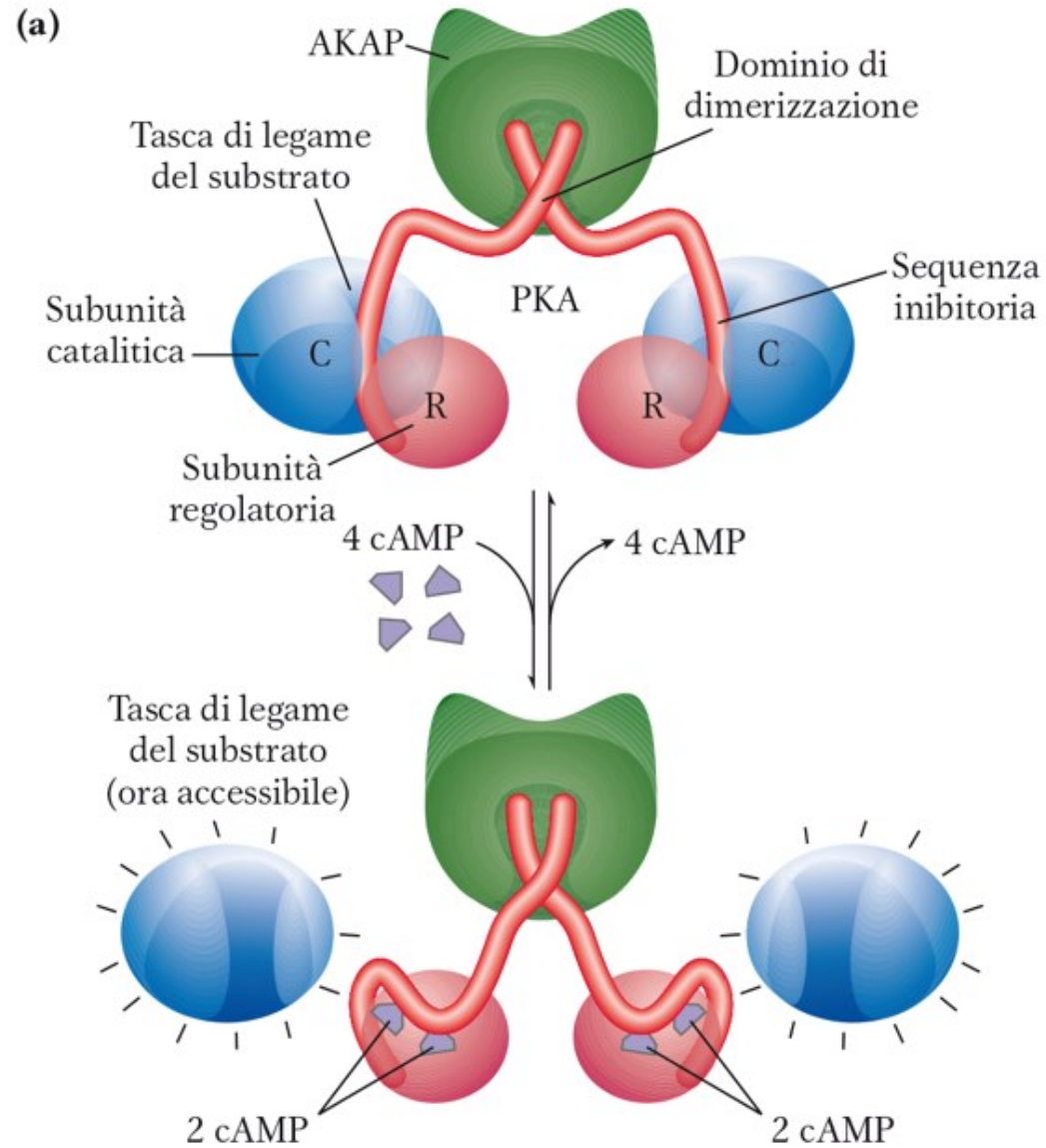
Trasduzione del segnale β AR



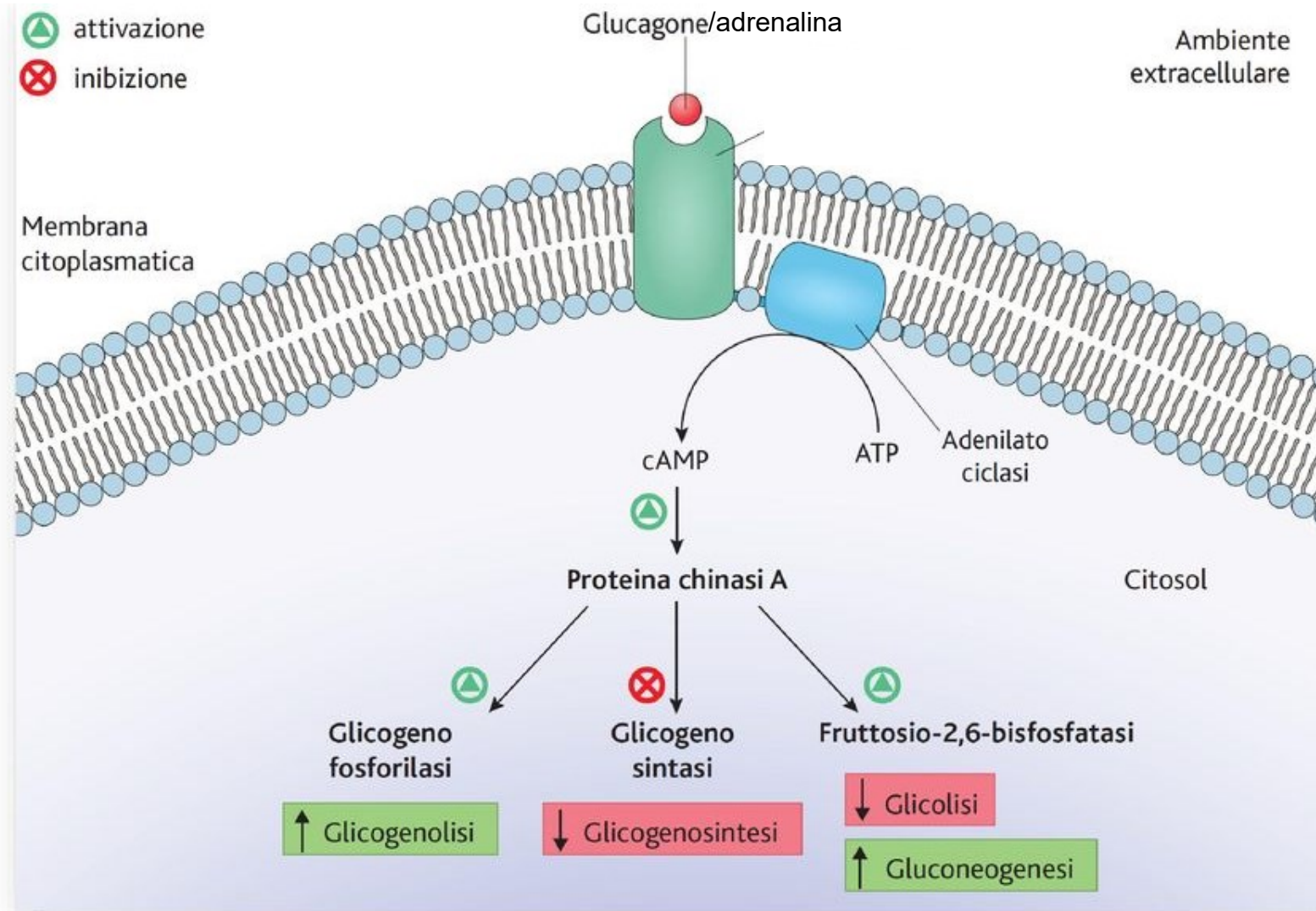
Restrizione spaziale della biosegnalazione



Chinasi dipendente da cAMP (PKA)



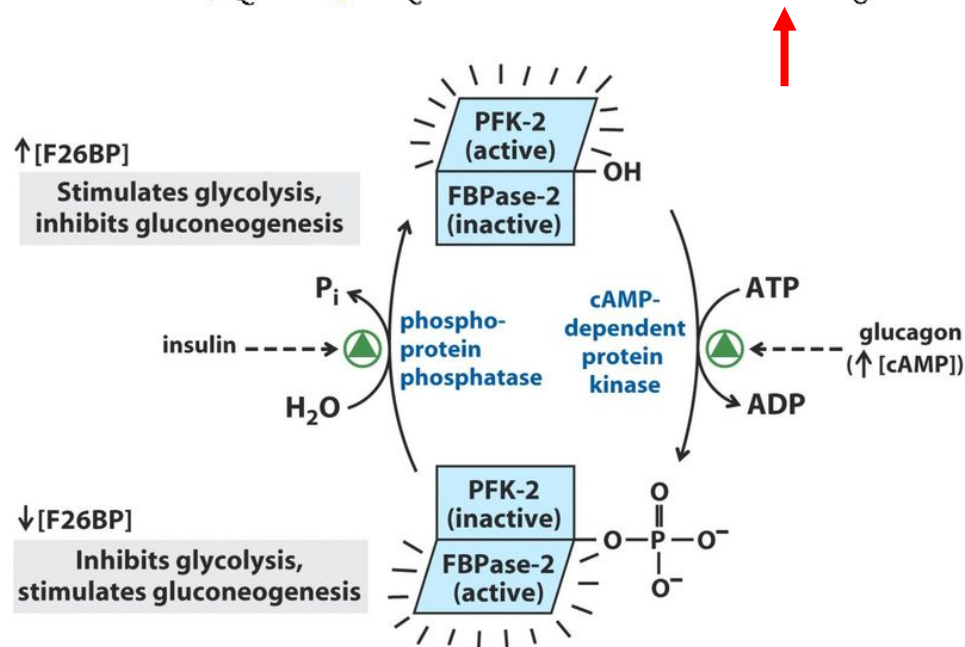
Effetti sul metabolismo del glucosio di adrenalina e glucagone



PKA e metabolismo del glucosio

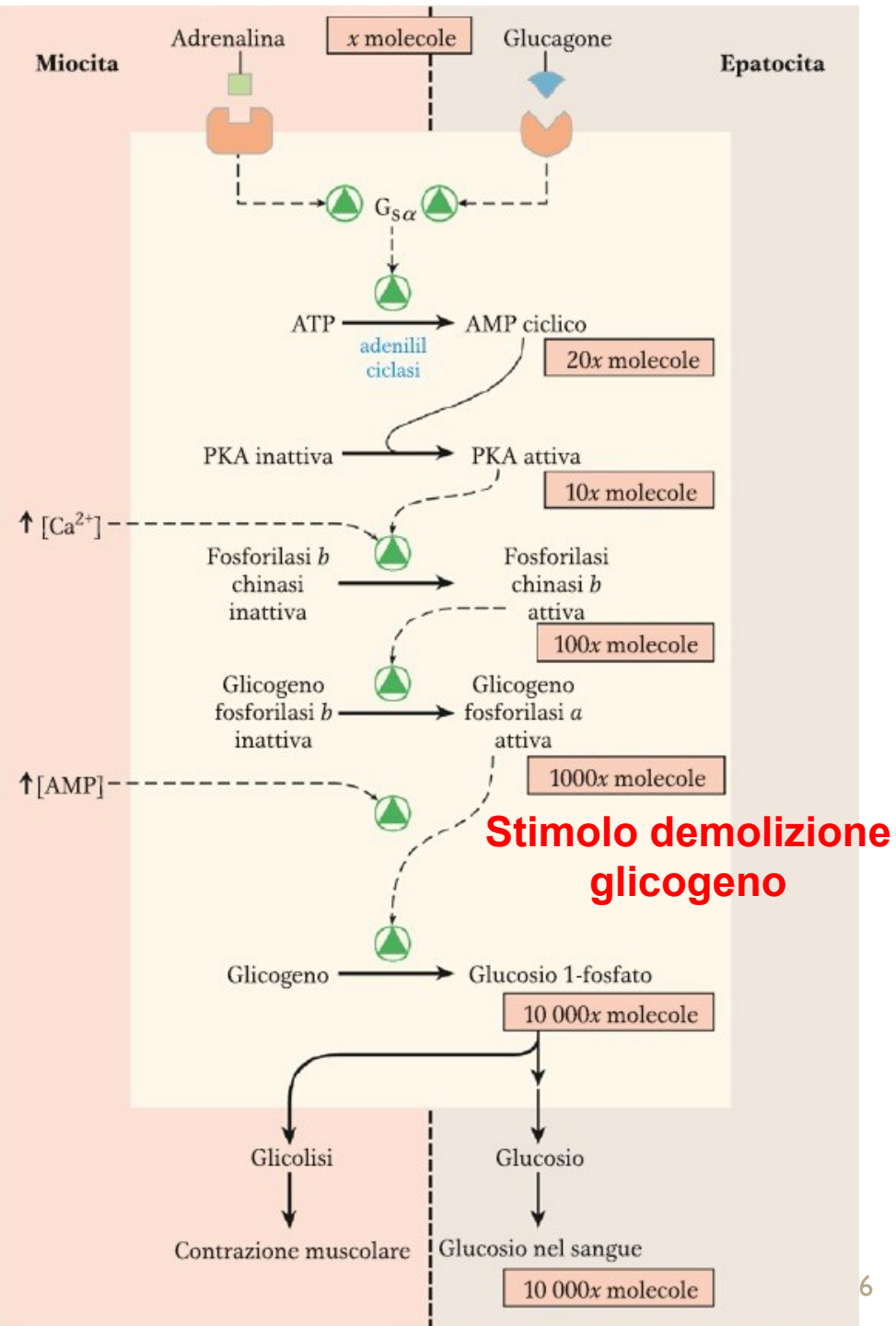
TABELLA 12.2 Alcuni enzimi e altre proteine regolati dalla fosforilazione cAMP-dipendente (da PKA)

Enzima/proteina	Sequenza fosforilata ^a	Via metabolica/processo regolato
Glicogeno sintasi	RASCTSSS inibizione	Sintesi del glicogeno
Fosforilasi b chinasi subunità α subunità β	VEFRRLSI } attivazione RTKRSGSV }	Demolizione del glicogeno
Piruvato chinasi (fegato di ratto)	GVLRRASVAZL inibizione	Glicolisi
Complesso della piruvato deidrogenasi (tipo L)	GYLRRASV inibizione	Da piruvato ad acetil-CoA
Lipasi ormone-sensibile	PMRRSV attivazione	Mobilizzazione dei triacilgliceroli e ossidazione degli acidi grassi
Fosfofruttochinasi-2/fruttosio 2,6-bisfosfatasi	LQRRRGSSIPQ	Glicolisi/gluconeogenesi




Effetti metabolici dell'adrenalina/glucagone

Amplificazione del segnale

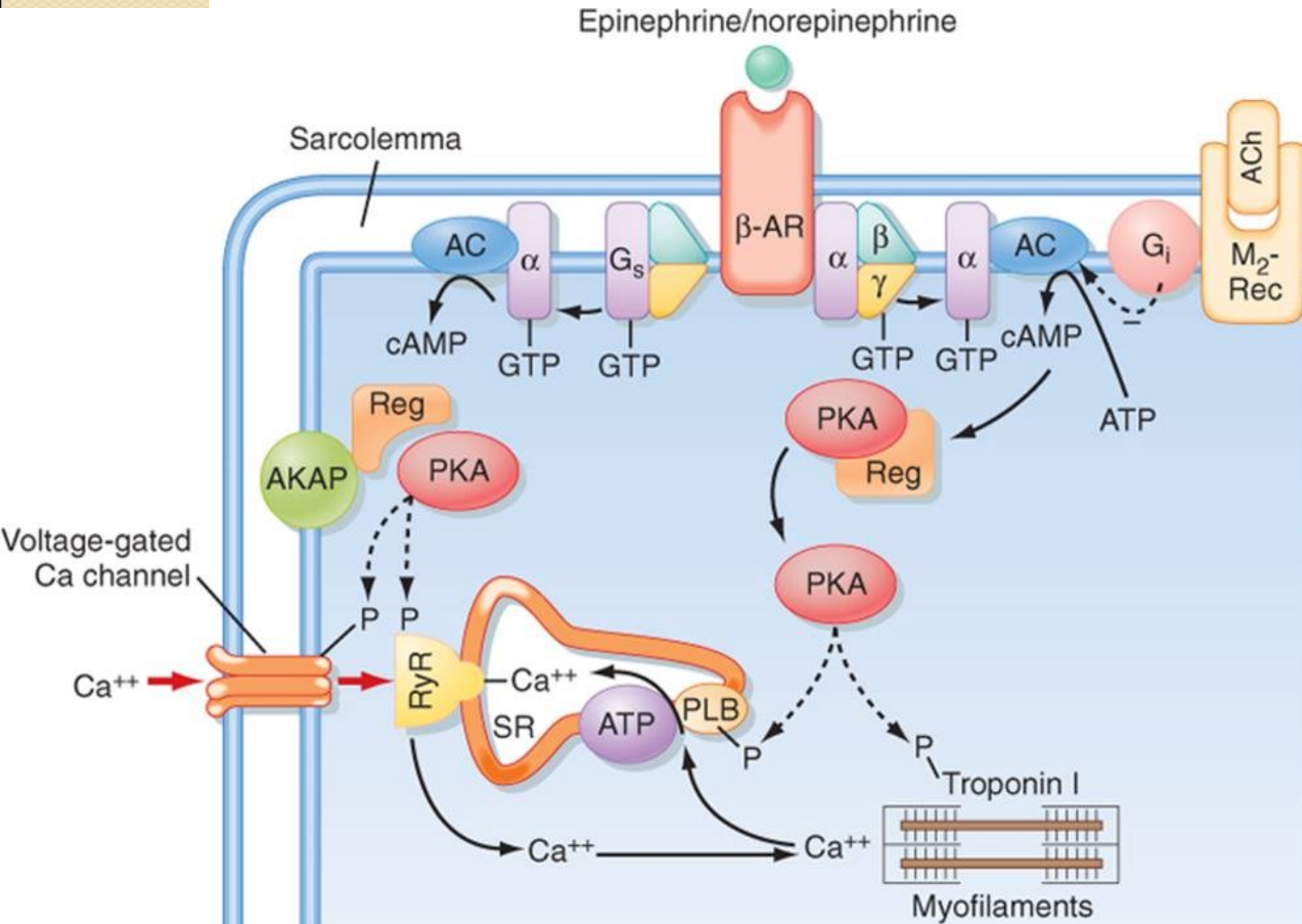


Substrati della PKA

TABELLA 12.2 Alcuni enzimi e altre proteine regolati dalla fosforilazione cAMP-dipendente (da PKA)

Enzima/proteina	Sequenza fosforilata ^a	Via metabolica/processo regolato
Glicogeno sintasi	RASCTSSS inibizione	Sintesi del glicogeno
Fosforilasi <i>b</i> chinasi subunità α subunità β	VEFRRLSI } RTKRSGSV } attivazione	Demolizione del glicogeno
Piruvato chinasi (fegato di ratto)	GVLRRASVAZL	Glicolisi
Complesso della piruvato deidrogenasi (tipo L)	GYLRRASV	Da piruvato ad acetil-CoA
Lipasi ormone-sensibile	PMRRSV	Mobilizzazione dei triacilgliceroli e ossidazione degli acidi grassi
Fosfofruttochinasi-2/fruttosio 2,6-bisfosfatasi	LQRRRGSSIPQ	Glicolisi/gluconeogenesi
Tirosina idrossilasi	FIGRRQSL	Sintesi di L-dopa, dopamina, noradrenalina e adrenalina
Istone H1	AKRKASGPPVS	Condensazione del DNA
Istone H2B	KKAKASRKESYSVYVYK	Condensazione del DNA
 Fosfolambano cardiaco (una pompa regolatrice cardiaca)	AIRRAST	[Ca ²⁺] intracellulare
Inibitore-1 della proteina fosfatasi-1	IRRRRPTP	Defosforilazione delle proteine
Sequenza consenso della PKA ^b	xR[RK] _x [ST]B	Molte

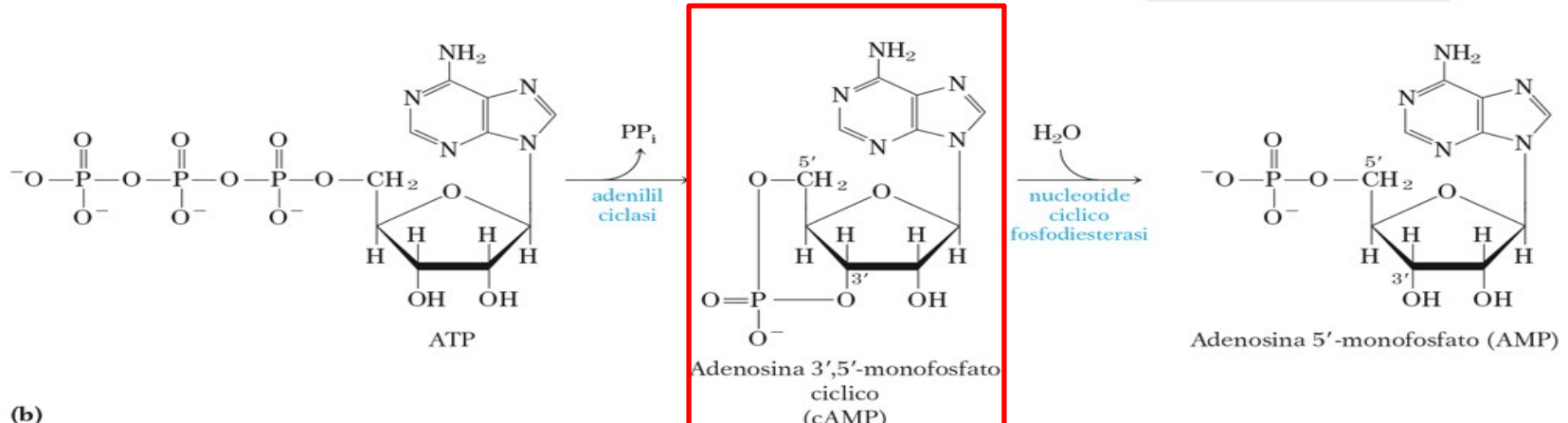
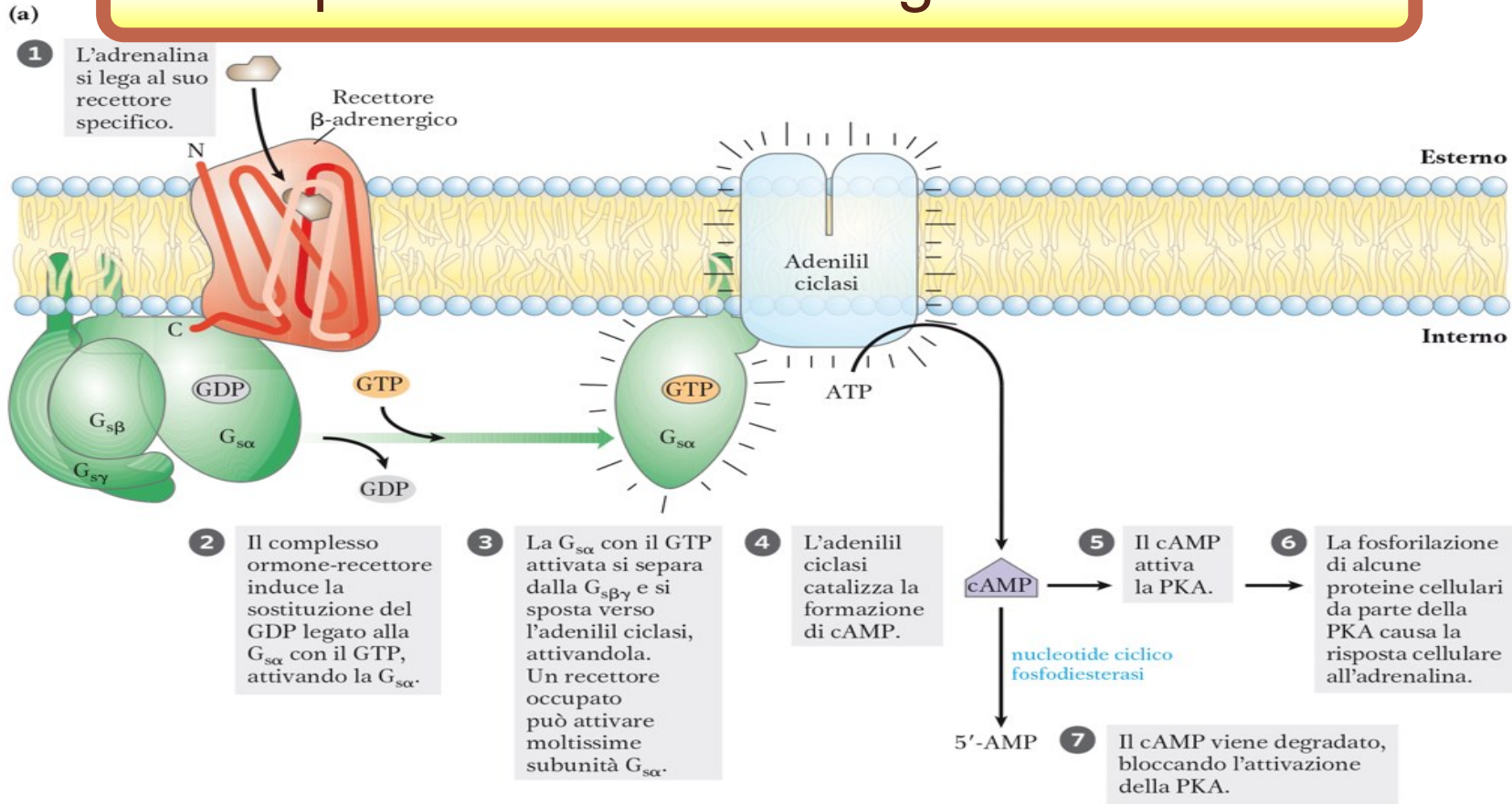
Effetti del signalling adrenergico sul cuore



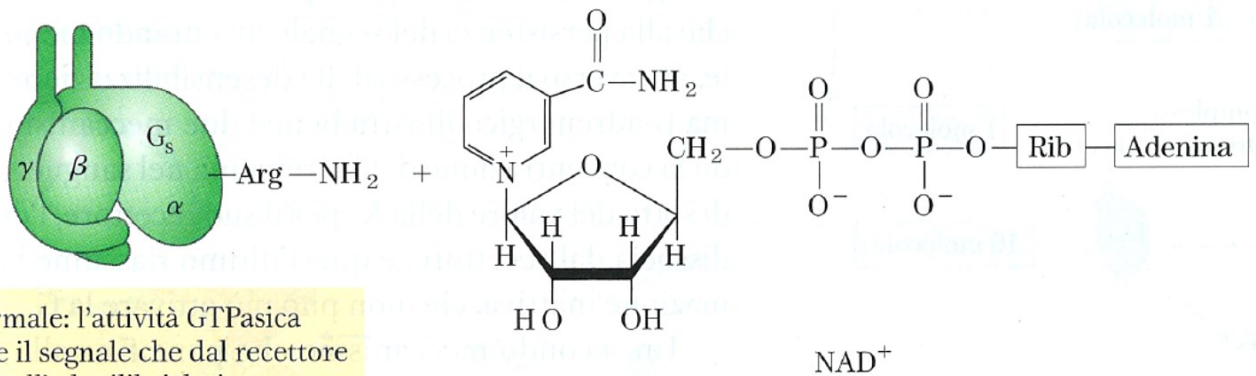
Catecholamine induces calcium influx into the sarcoplasmic reticulum

therefore increases both inotropy and lusitropy.

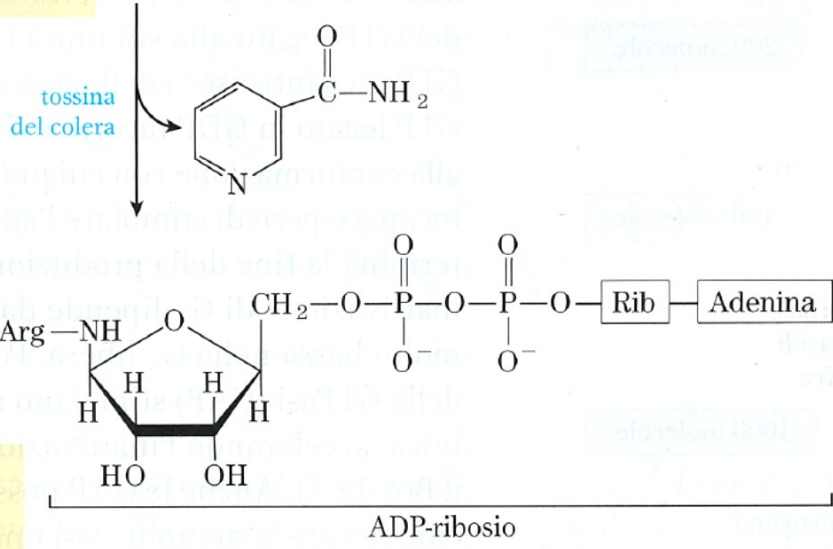
Le proteine G sono target di tossine



Effetti della tossina colerica



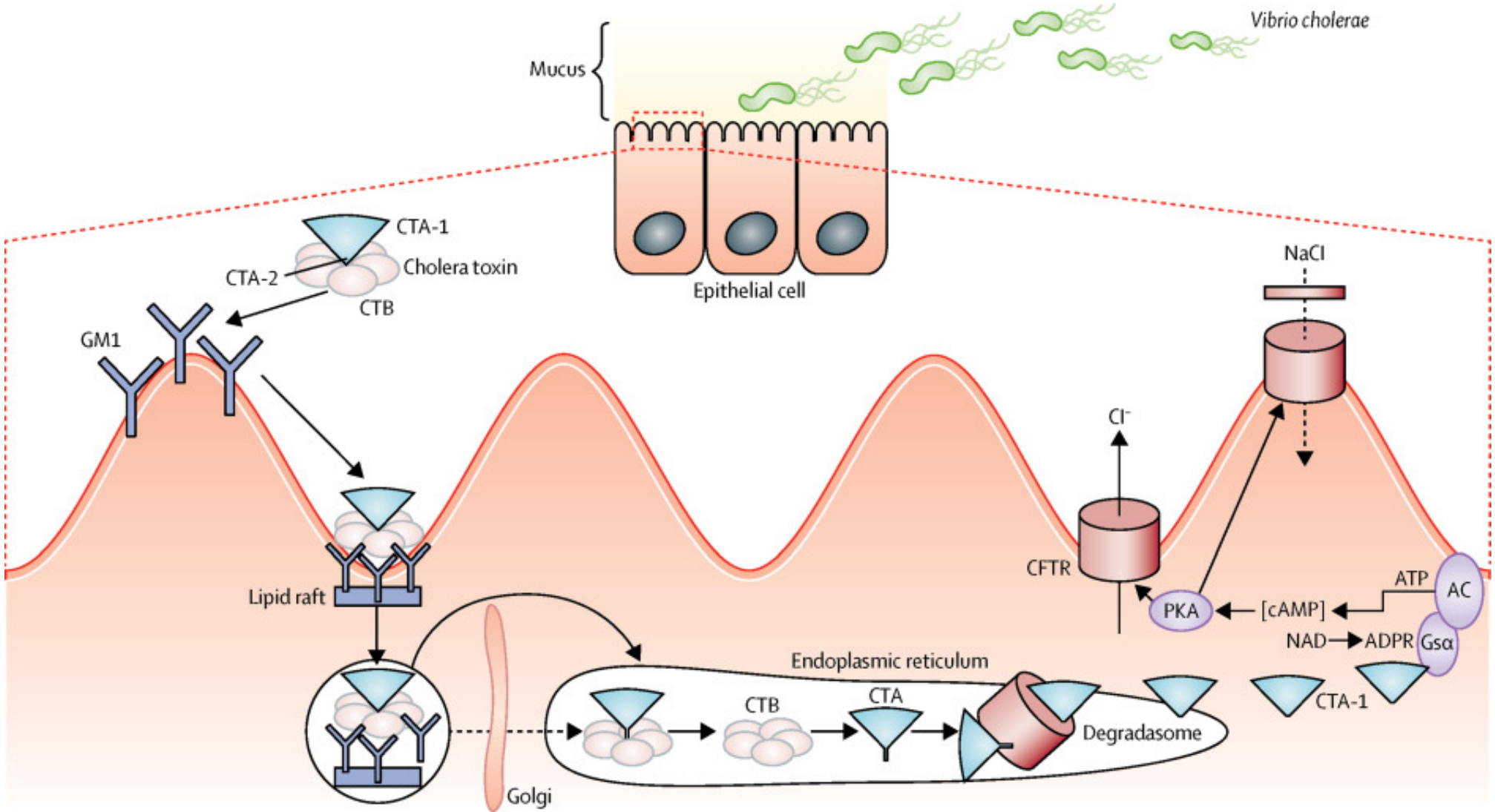
G_s normale: l'attività GTPasica spegne il segnale che dal recettore giunge all'adenilil ciclasi.



G_s ADP-ribosilata: l'attività GTPasica è inattivata; la G_s attiva costantemente l'adenilato ciclasi.

INATTIVAZIONE DELL'ATTIVITÀ GTPasica

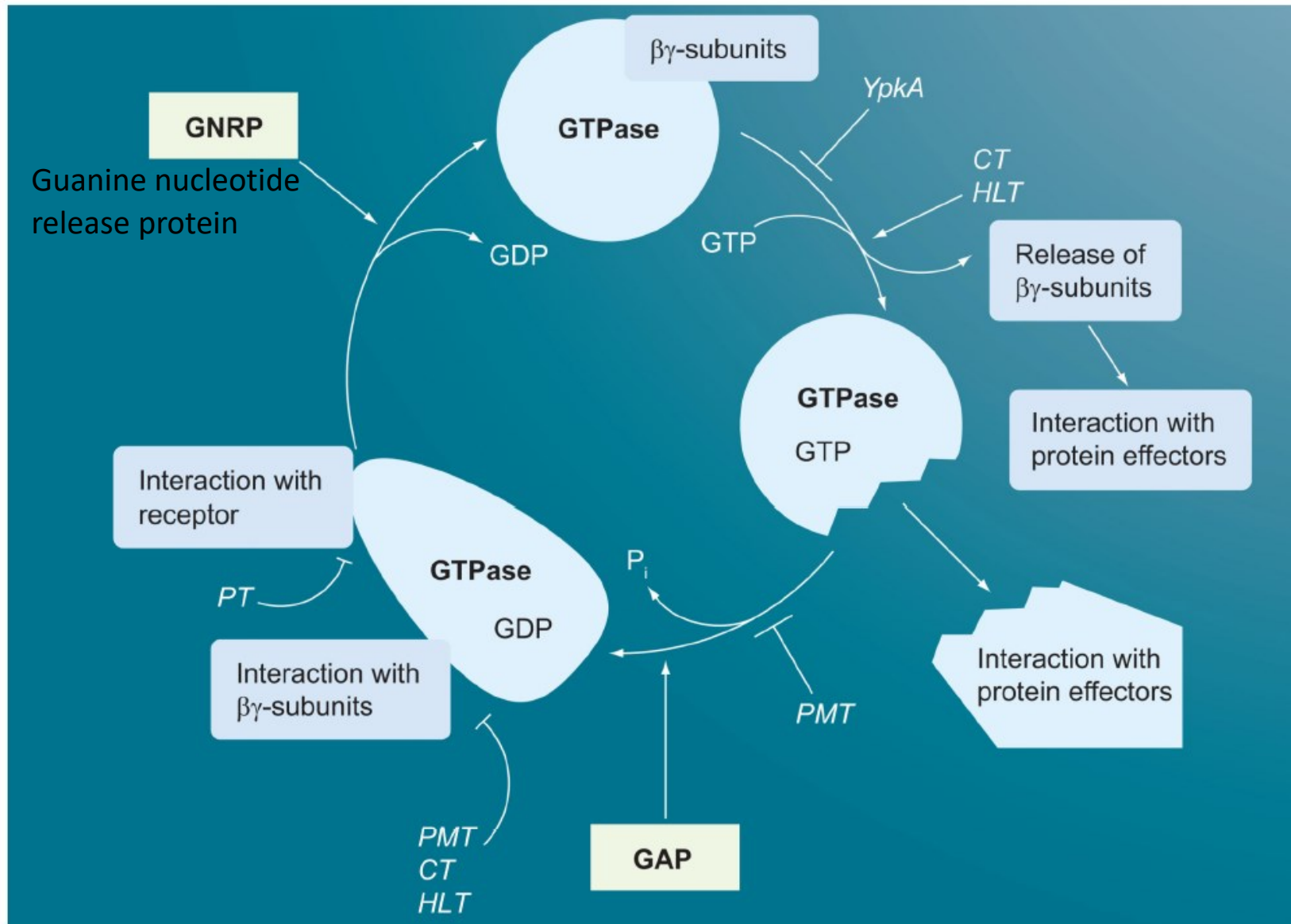
Effetti della tossina colerica



Proteine G e tossine

G-protein targets	Modulating toxins	Modification	Effect on G protein	Ref.
<i>Small GTPases</i>				
RhoA, Rac1, Cdc42	TcdA, TcdB, TcsH, TcsL, Tcna	Monoglucosylation	Inactivation	[59,60]
Rap1, Rap2	TcdA, TcsL	Monoglucosylation	Inactivation	[61,62]
RhoA, RhoB, RhoC	clostridial C3	ADP-ribosylation	Inactivation	[51]
Ras	ExoS	ADP-ribosylation	Inactivation	[79–82]
RhoA, Rac1, Cdc42	ExoS, ExoT, SptP, YopE	GAP-like activity	Inactivation	[72–74]
Rab1	LepB	GAP-like activity	Inactivation	[86]
RhoA, Rac1	YpkA, YopO	GDI-like activity	Inactivation	[85]
RhoA, Rac1, Cdc42	YopT, Avr/PhpB	Proteolysis	Inactivation	[61]
RhoA, RhoB, RhoC, Rac1, Cdc42	MARTX	Unknown	Inactivation	[92]
RhoA, Rac1, Cdc42	SopE, SifA, SifB, lpgB1, lpgB2, Map, EspM, EspT	GEF-like activity	Activation	[69]
Arf	RaF	GEF-like activity	Activation	[71]
Rab1	DrrA/SidM	GEF-like activity	Activation	[86–88]
Rab1	DrrA/SidM	GDF-like activity	Activation	[86–88]
RhoA, Rac1, Cdc42	CNF1, CNF2, CNF3	Deamidation [†]	Activation	[19]
RhoA	CNFY	Deamidation [†]	Activation	[100]
RhoA, Rac1, Cdc42	DNT	Transglutamination [‡]	Activation	[19]
<i>Heterotrimeric Gα subunits</i>				
G _i , G _o , G _t	PT	ADP ribosylation	Inactivation [§]	[45,48]
G _q	YpkA	Phosphorylation	Inactivation	[84]
G _s , G _{olf} , G _t	CT, HLT	ADP ribosylation	Activation [§]	[45,48]
G _q , G ₁₃ , G _i	PMT	Deamidation	Activation [§]	[9,21,32,112,113,135]
<i>Large, multidomain GTPases</i>				
EF-2	DT, ExoA	ADP ribosylation	nactivation	[41]

GTPase cycle of heterotrimeric G proteins and points of toxin interactions



YpKA: *Yersinia pseudotuberculosis* serotype I;

CT: Cholera toxin;

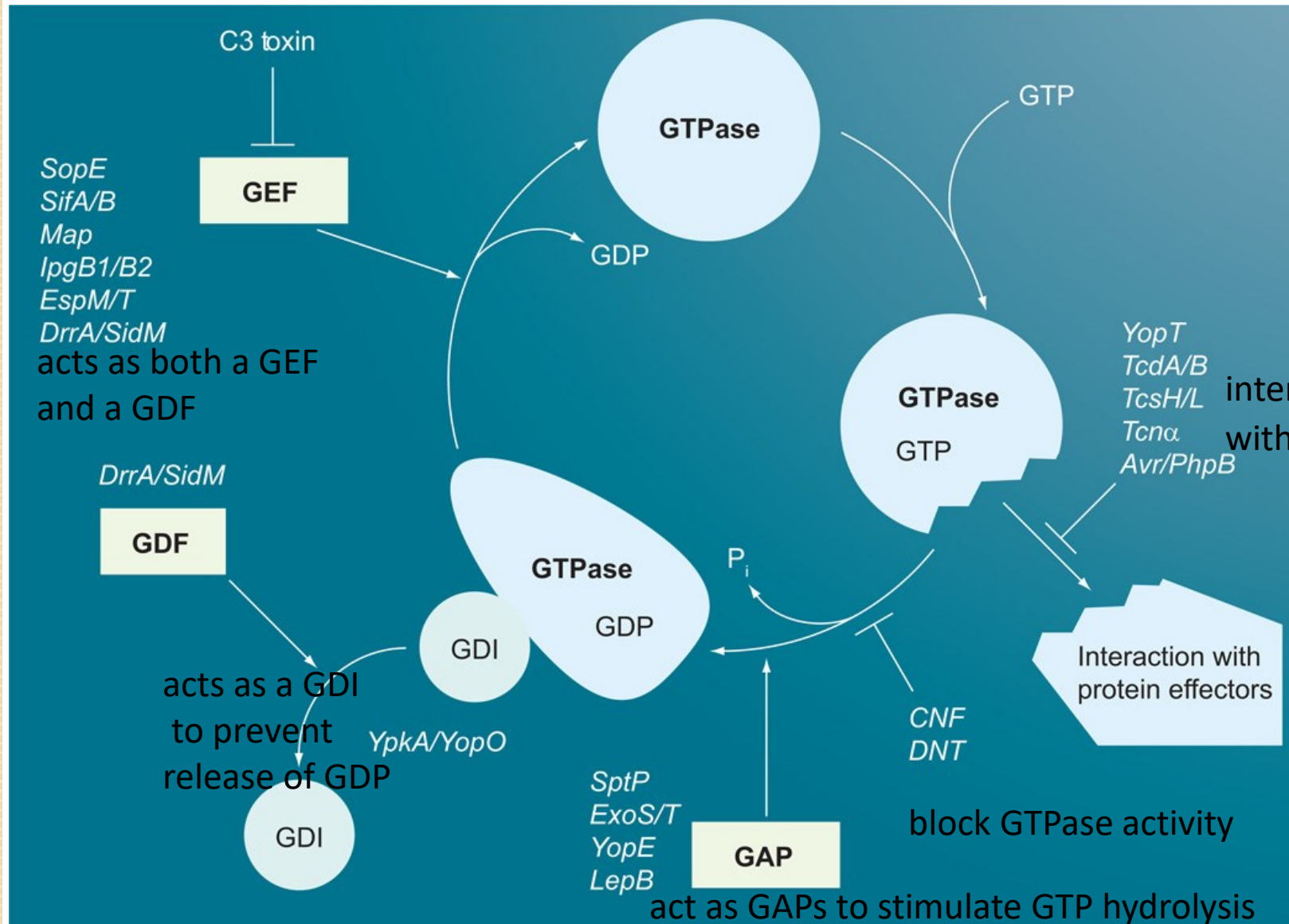
HLT: Heat-labile enterotoxins;

PMT: *Pasteurella multocida* toxin;

PT: Pertussis toxin.

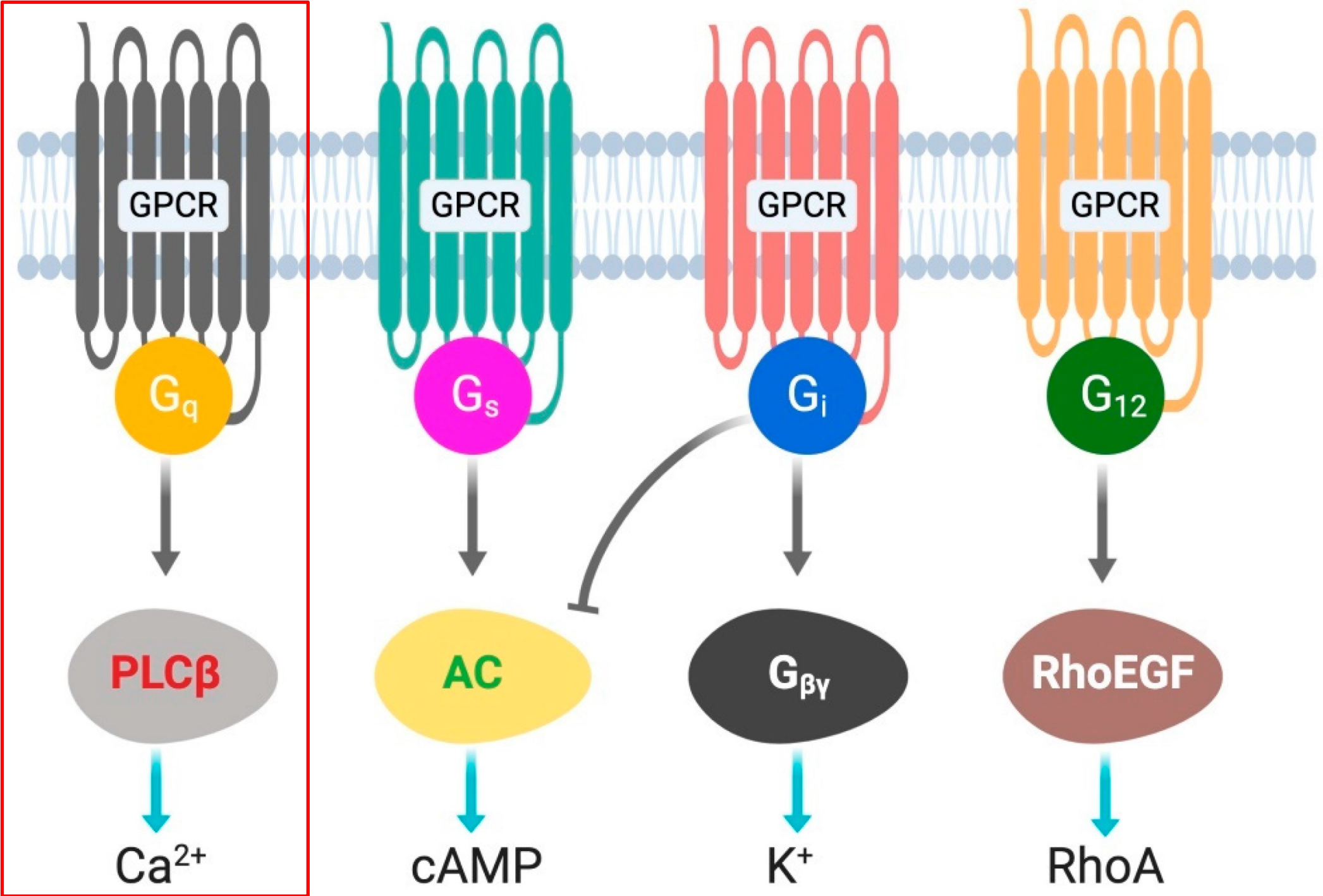
Figure 2. GTPase cycle of heterotrimeric G proteins and points of toxin interactions

GTPase cycle of small G proteins and points of toxin interactions

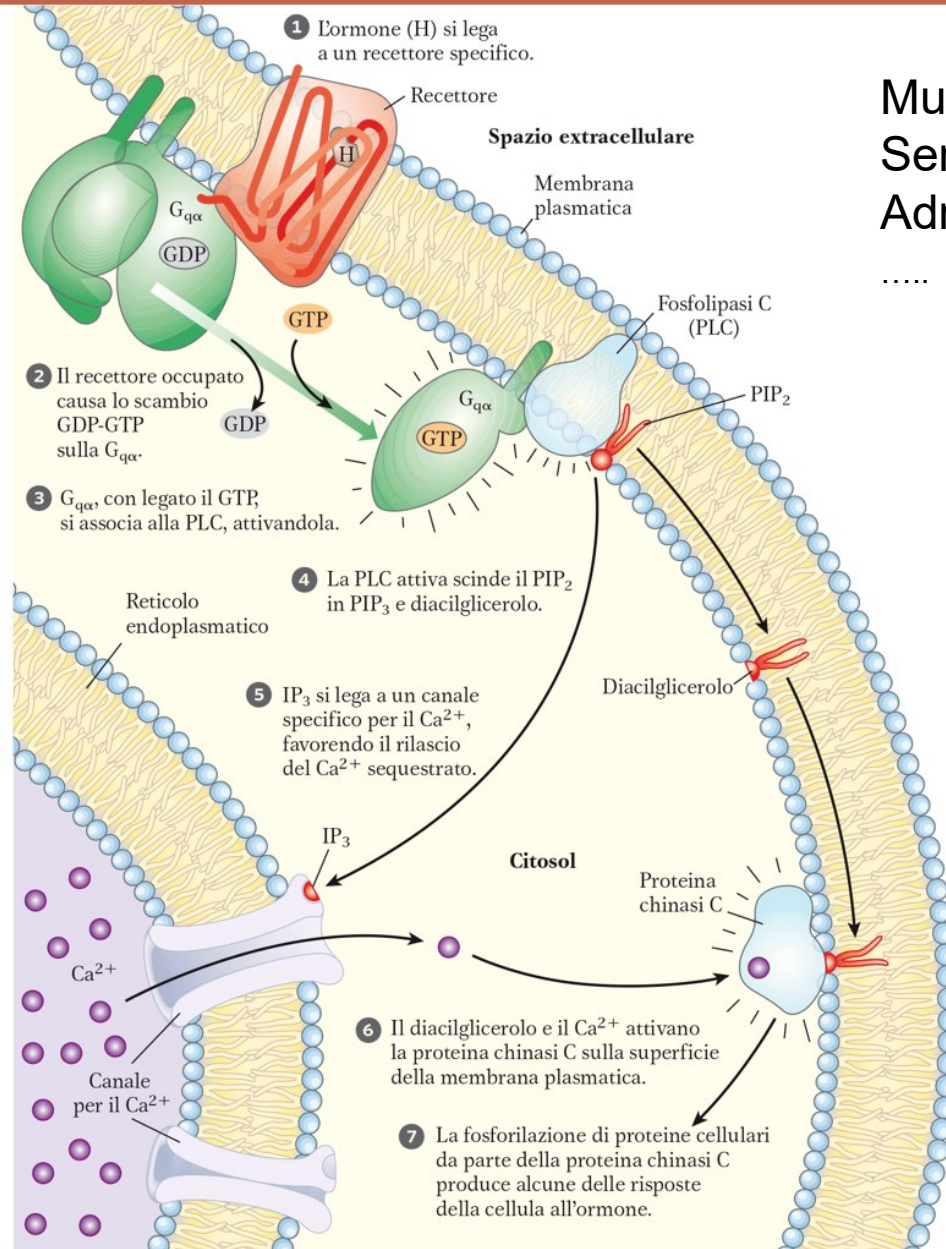


interfere with the GTPase interaction with effectors.

block GTPase activity
act as GAPs to stimulate GTP hydrolysis



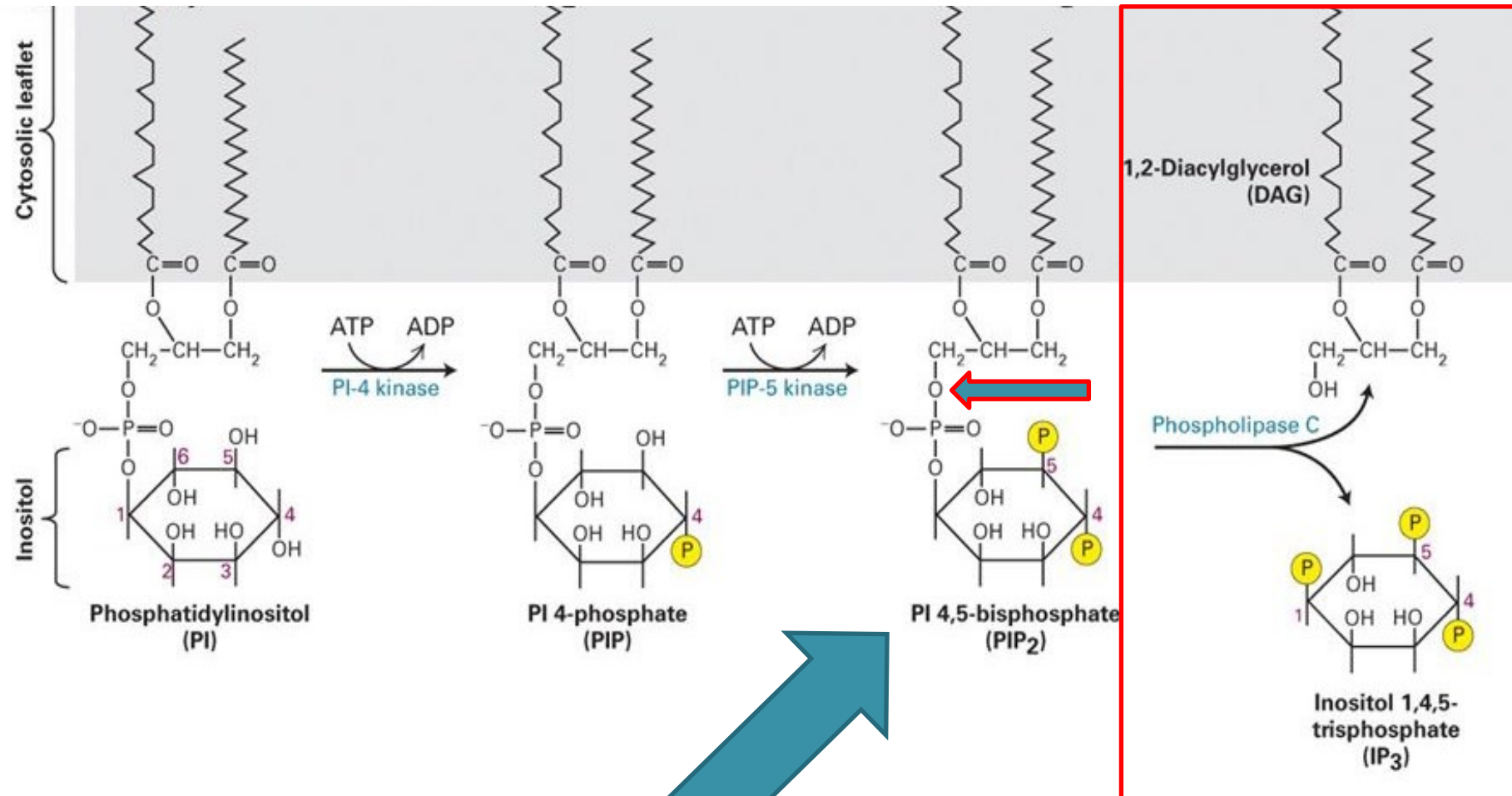
Recettori accoppiati a Gq



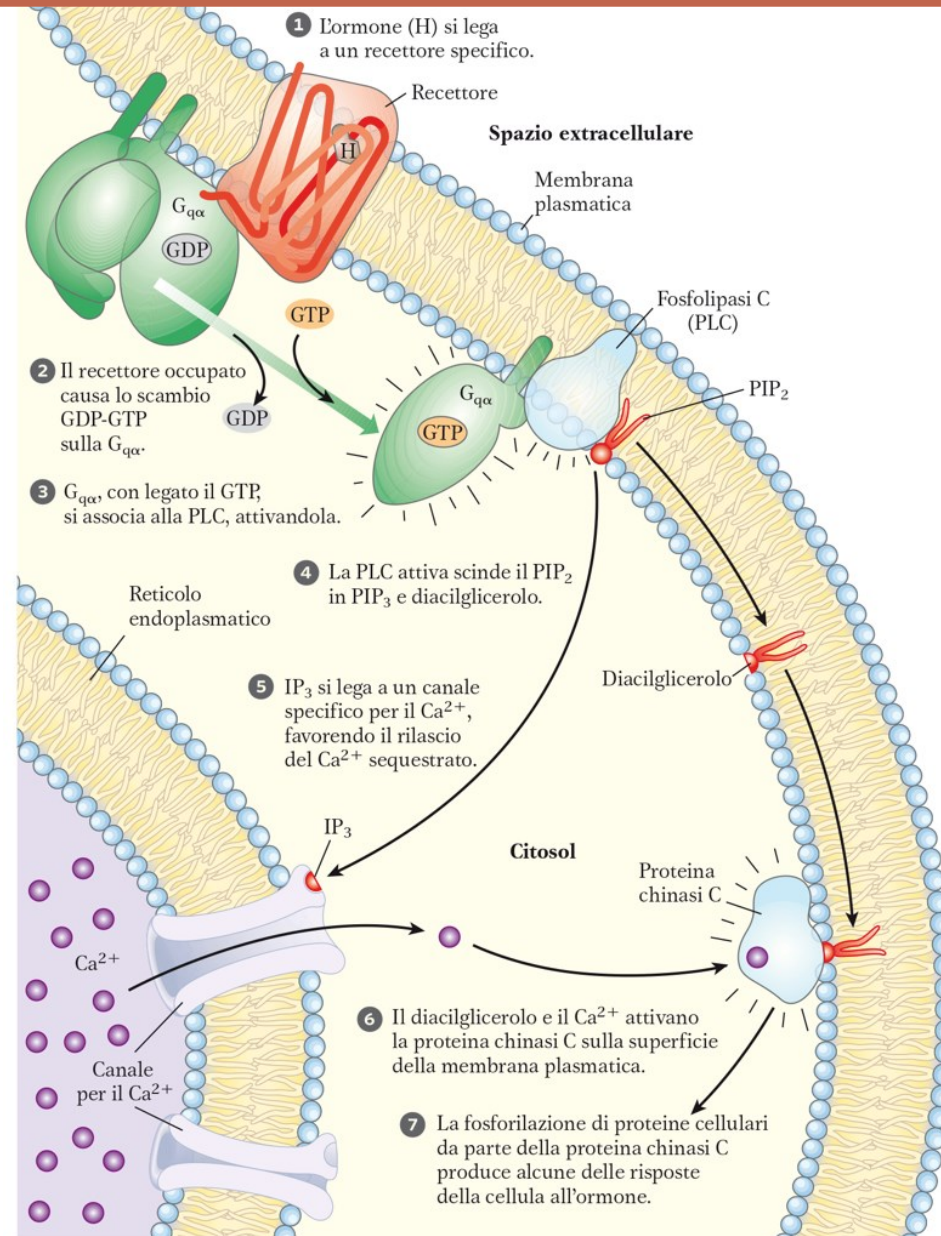
Muscarinico M3
Serotonergici 5-HT_{2a,b,c}
Adrenergico Alpha1

.....

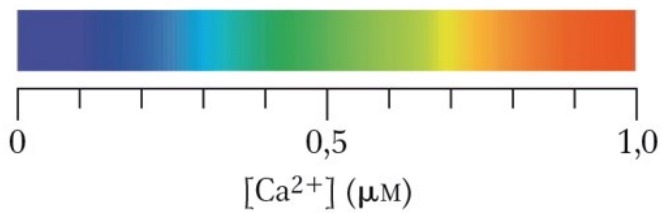
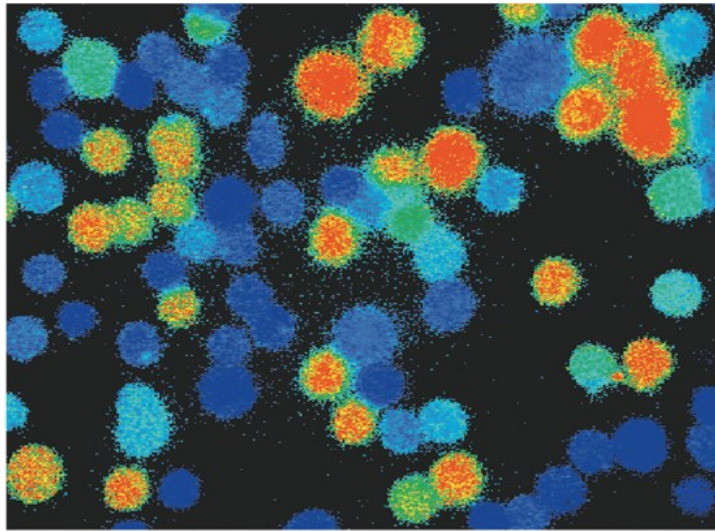
Produzione di IP3



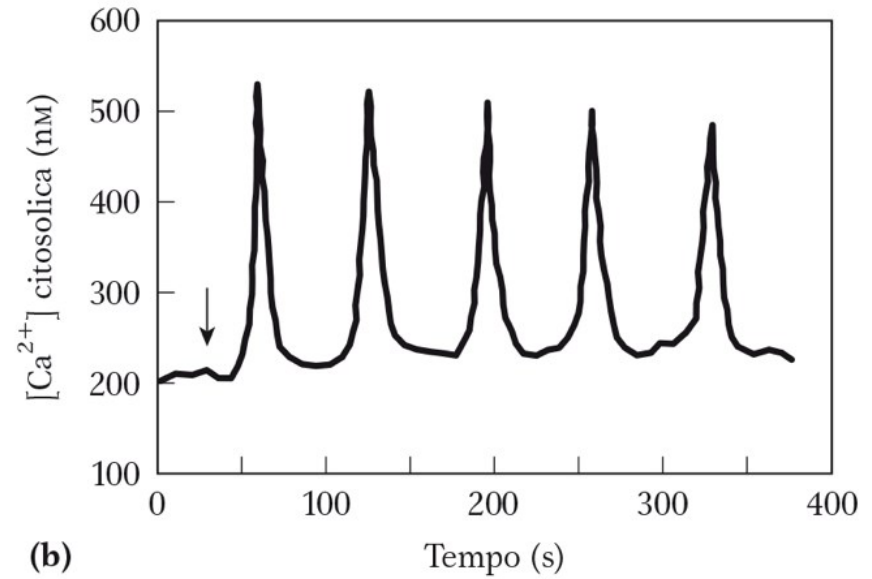
Recettori accoppiati a Gq



Peculiarità del rilascio di calcio

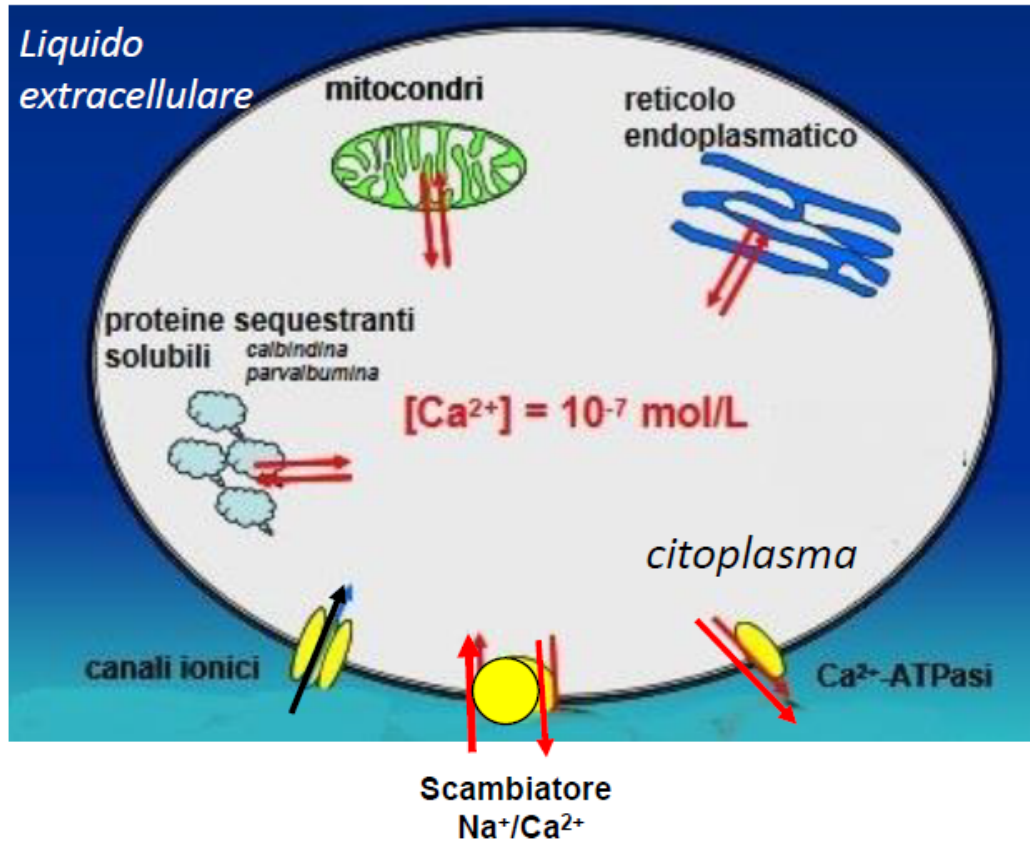


(a)



(b)

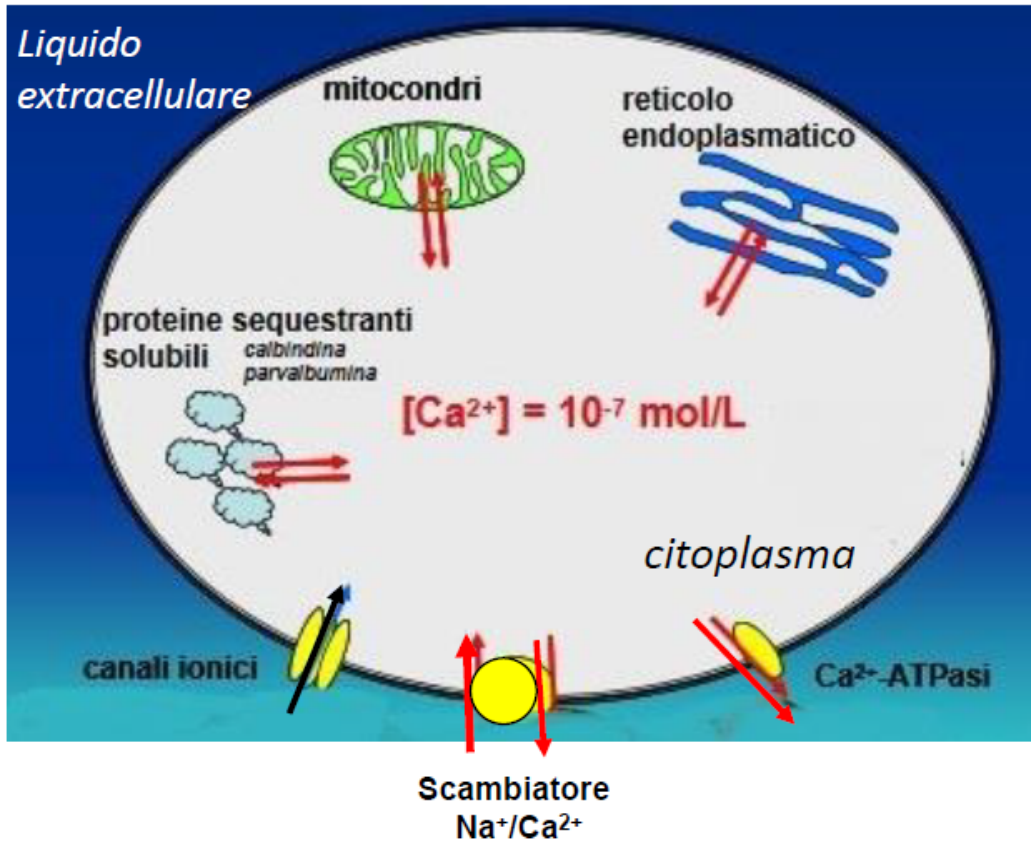
Gli ioni Ca^{2+} come secondi (o terzi messaggeri)



La concentrazione intracellulare di Ca^{2+} è finemente regolata in quanto il Ca^{2+} rappresenta un messaggero intracellulare. Infatti, transitori cambiamenti della sua concentrazione intracellulare rappresentano segnali per la cellula per l'attivazione di risposte quali: l'esocitosi, la contrazione muscolare, l'apertura o chiusura di canali ionici, ecc.

Pertanto, il mantenimento di una bassa concentrazione citoplasmatica di Ca^{2+} fa sì che anche piccoli flussi di Ca^{2+} in ingresso rappresentino significativi segnali intracellulari.

Gli ioni Ca^{2+} come secondi (o terzi messaggeri)



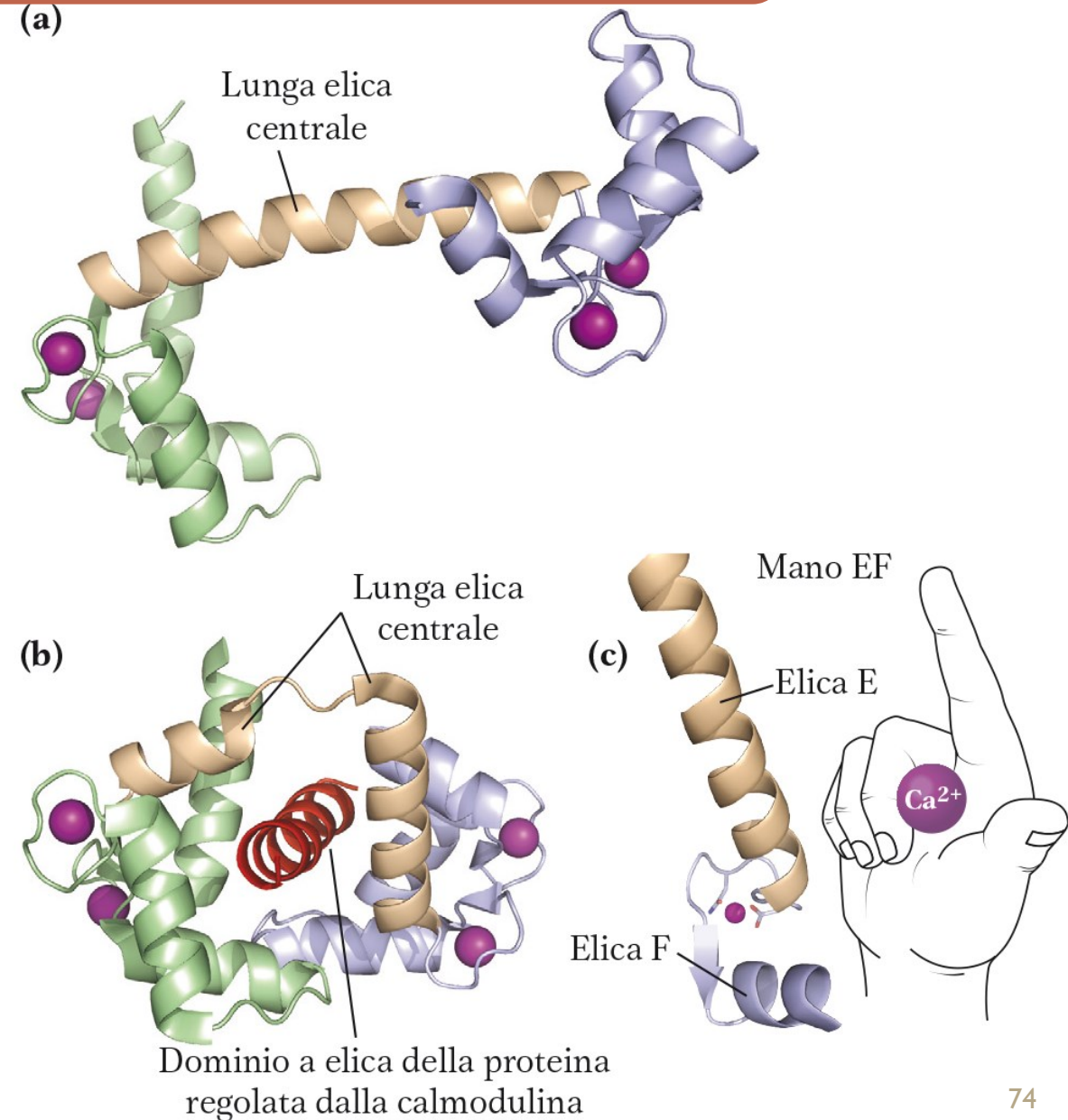
La concentrazione citoplasmatica di calcio della cellula eucariotica a riposo si aggira intorno a 10^{-7}M nonostante una concentrazione extracellulare di 1-2 mM.

Il mantenimento di una tale differenza di concentrazione tra l'interno e l'esterno della cellula è il risultato dell'azione coordinata di differenti sistemi che comprendono:

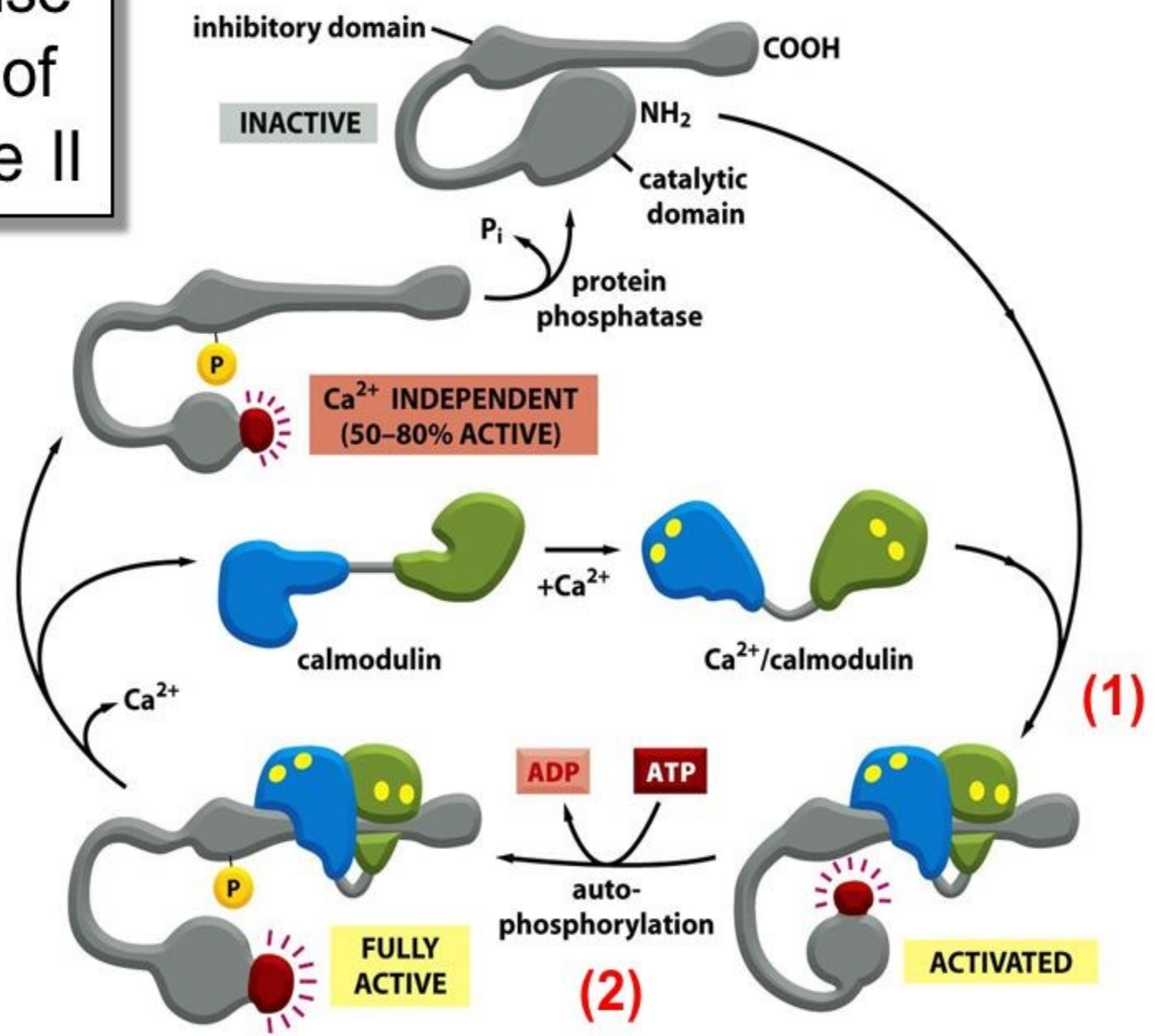
- trasporti attivi primari e secondari che provvedono ad estrudere il Ca^{2+} dalla cellula e ad accumularlo in depositi intracellulari (reticolo endoplasmico, mitocondri).
- sistemi tampone della concentrazione di Ca^{2+} rappresentati da proteine leganti il Ca^{2+} (*Ca^{2+} binding proteins*), di cui la più nota è la calmodulina.

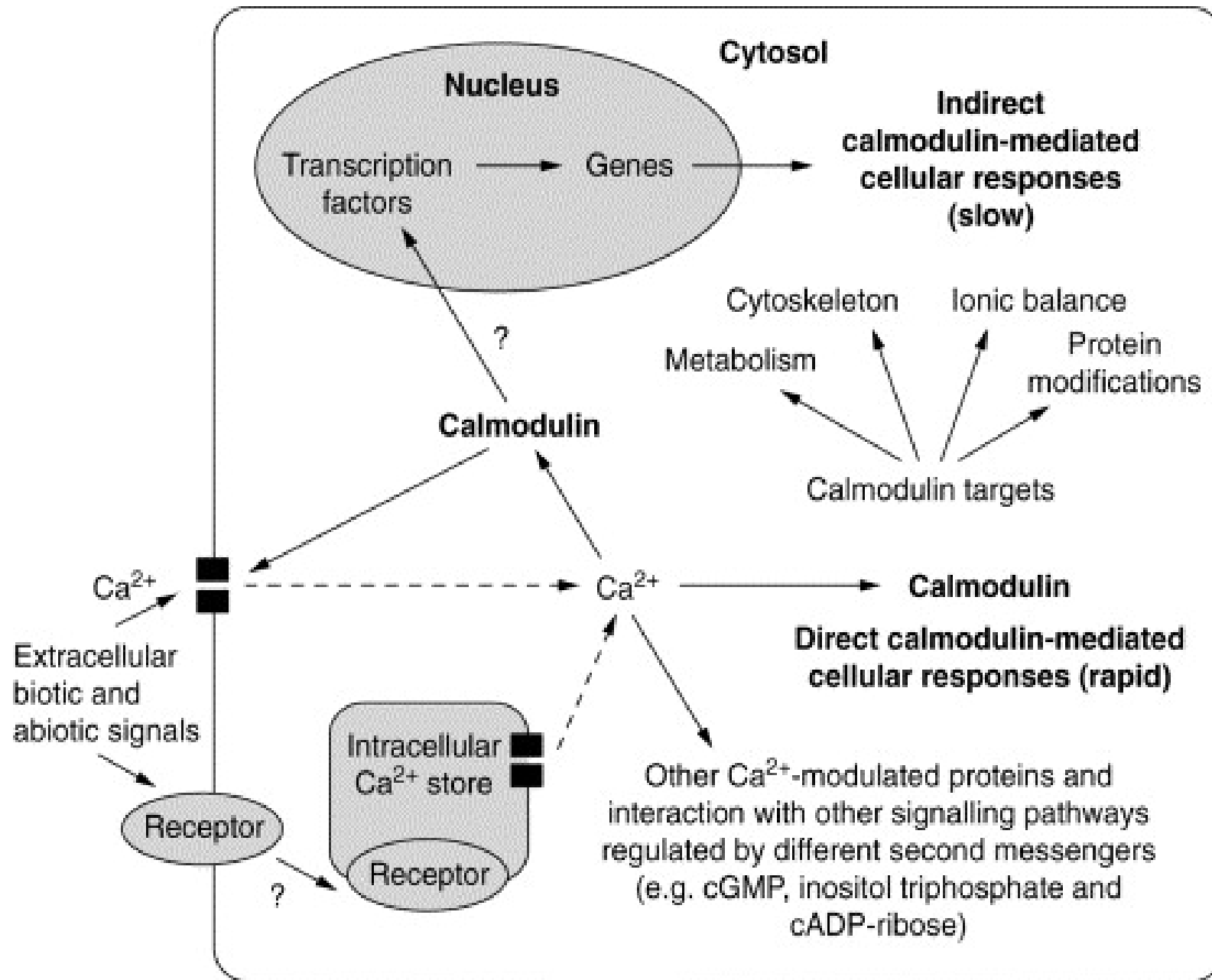
La calmodulina un effettore del Ca^{2+}

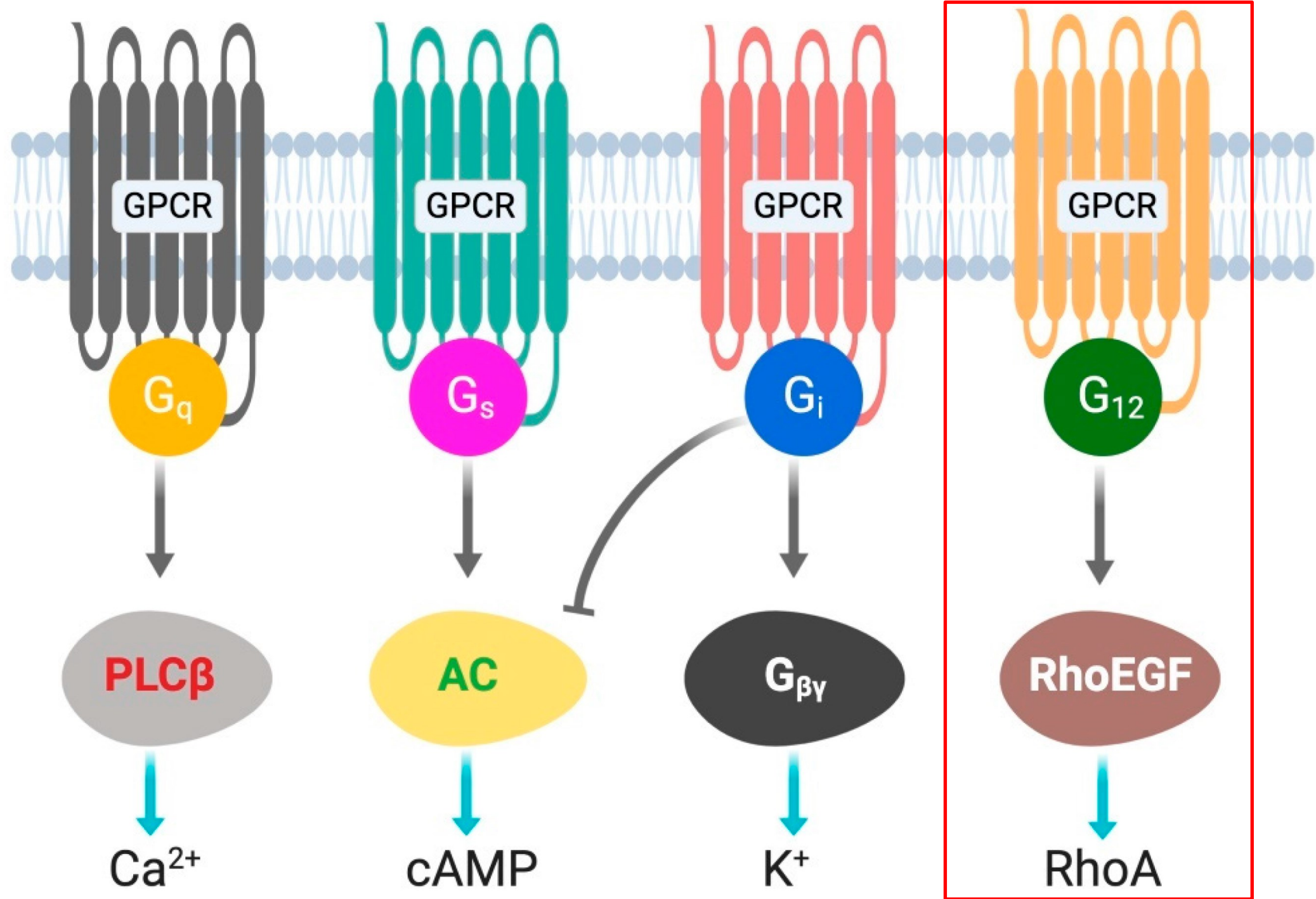
- In numerosissime vie di segnalazione l'azione del calcio è mediata dalla calmodulina.
- La calmodulina è una piccola proteina regolatrice attivata dal calcio presente in tutte le cellule eucariotiche.
- È costituita da due domini globulari, ciascuno dei quali è in grado di legare due ioni Ca^{2+} ; ciò conferisce alla calmodulina la capacità di legare complessivamente 4 ioni Ca^{2+} .
- L'interazione con il calcio provoca una notevole modificazione conformazionale in seguito alla quale la proteina viene convertita nella sua forma attiva, in cui è capace di interagire con diversi tipi di proteine bersaglio.
- In alcuni casi il bersaglio è costituito da protein-chinasi che, a loro volta, attivano o disattivano altri bersagli mediante aggiunta di gruppi fosforici. Altri bersagli, come la pompa Ca^{2+} -ATPasi e alcune proteine che regolano l'assemblaggio dei microtubuli, sono sottoposte a regolazione per interazione diretta col complesso Ca^{2+} /calmodulina.



The stepwise activation of CaM-kinase II





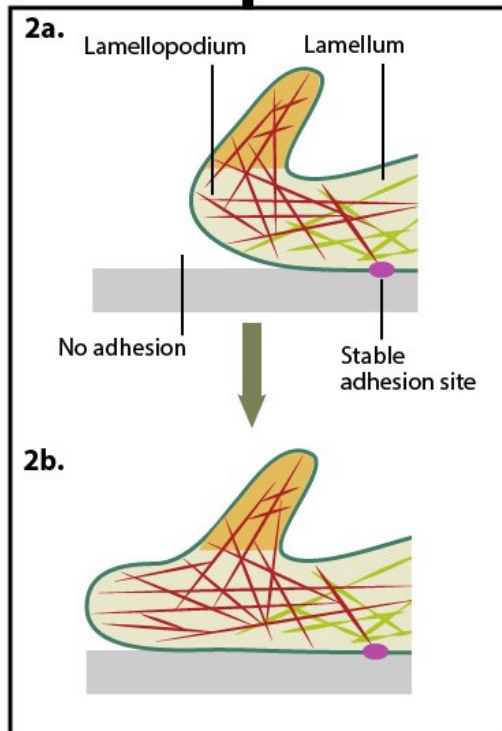
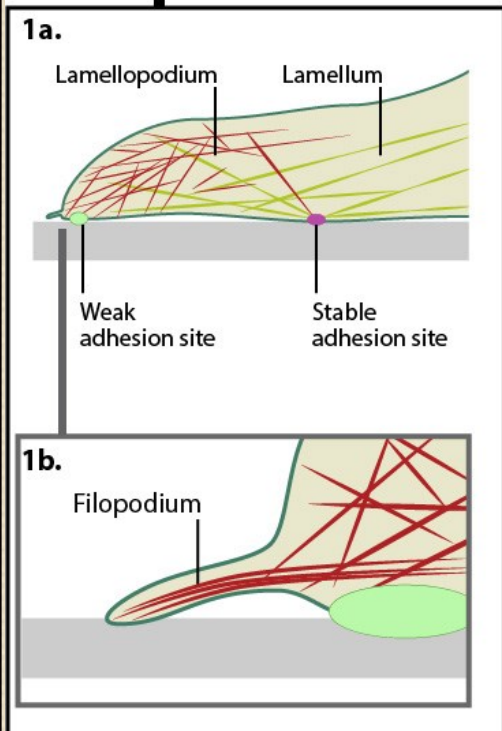
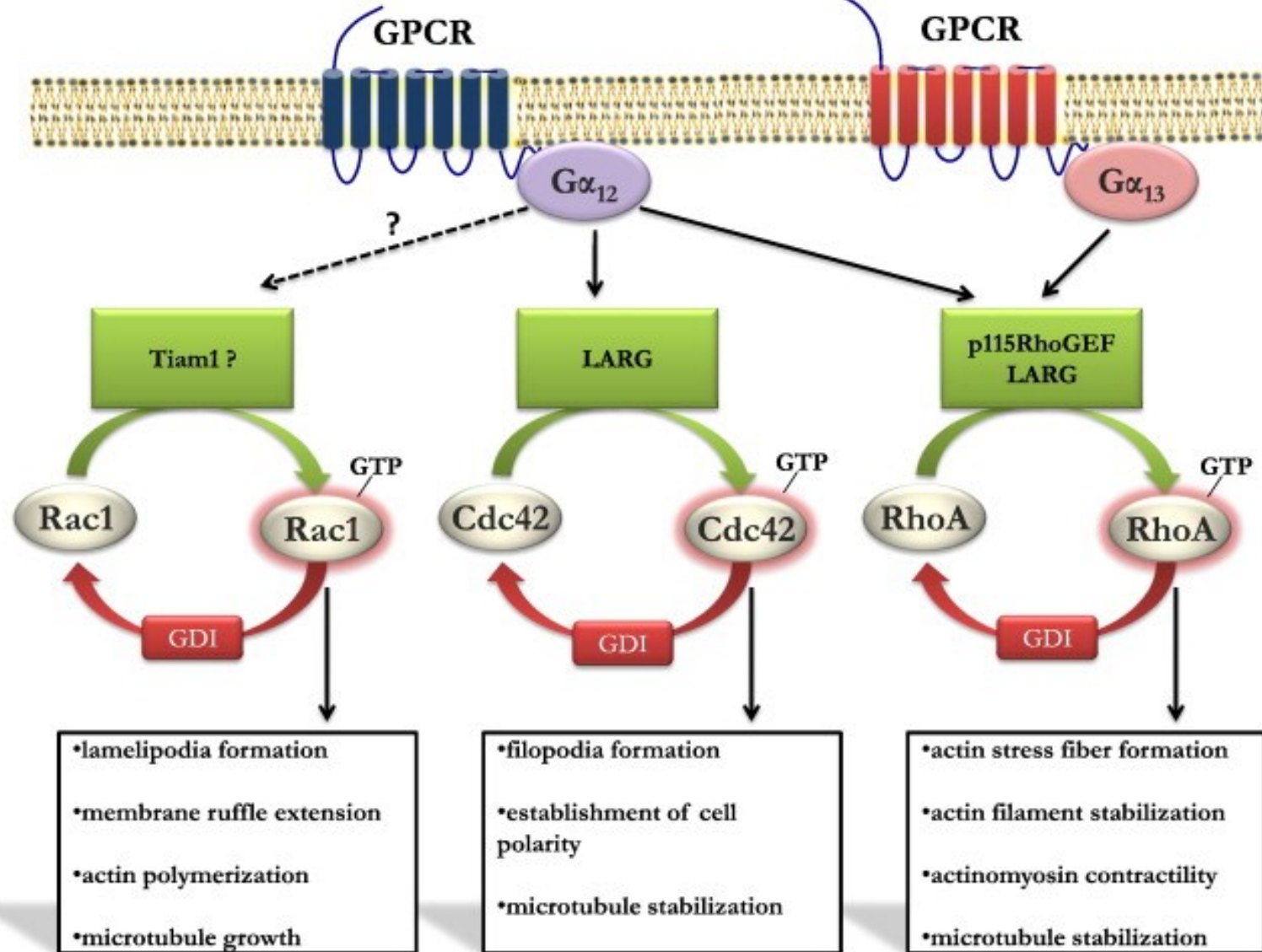
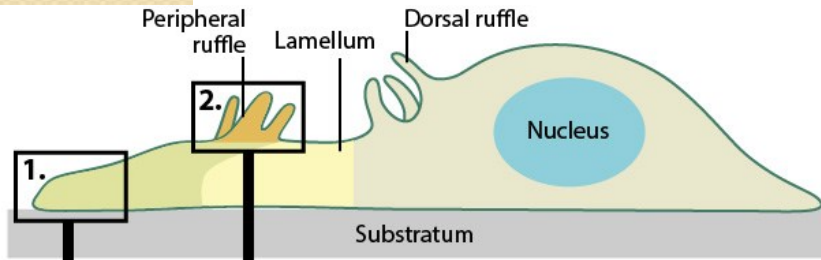
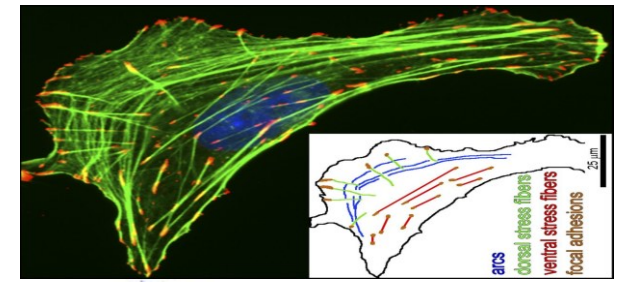


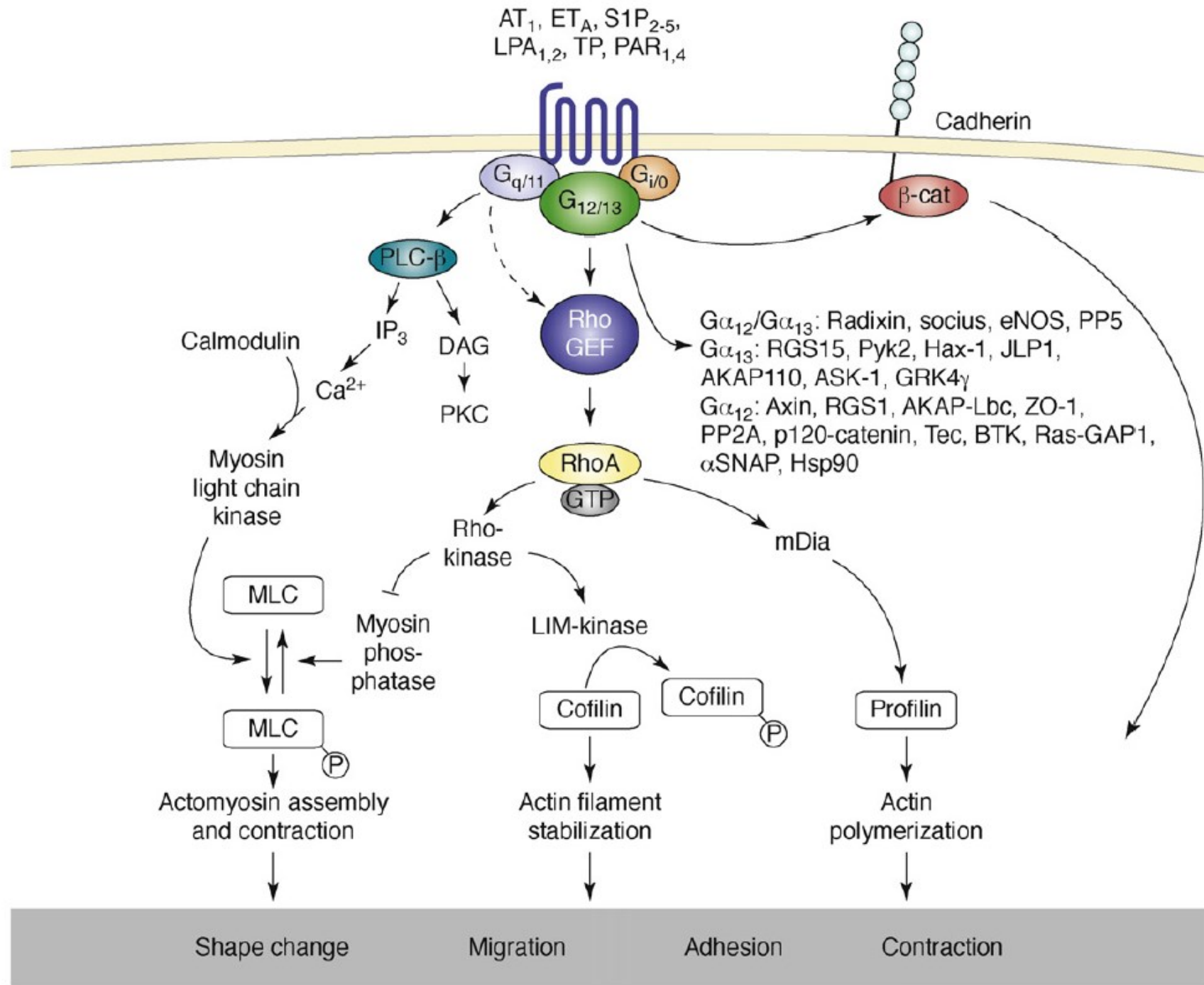
Recettori accoppiati a G12/13

Table 1 G $\alpha_{12/13}$ -associated GPCRs and physiological functions.

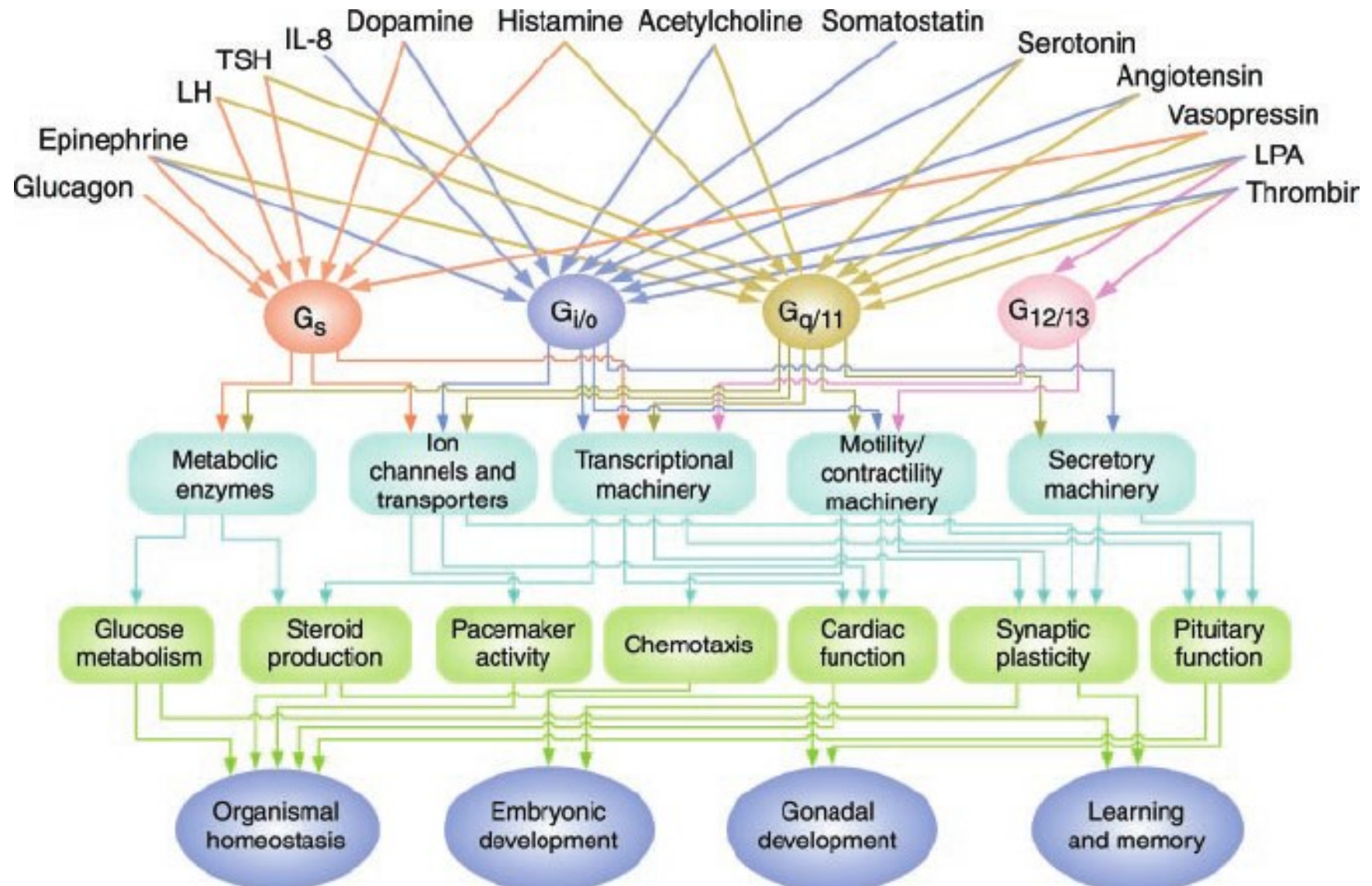
Receptors	G proteins	Functions	References
Sphingosine 1-phosphate			
S1P2/S1P3	G $\alpha_{12/13}$	Stress fiber formation	133
S1P1/S1P3/S1P5	G α_{12}	Inflammation	62
S1P3	G $\alpha_{12/13}$	Inflammation	134
S1P2	G $\alpha_{12/13}$	Myofibroblast contraction	135
S1P3	G α_{13}	Cardioprotection	136
S1P receptor	G α_{12}	Hepatic stellate cell activation	45
Thrombin			
PAR1	G α_{12}	Monocyte migration	63
PAR1	G α_{13}	Cell transformation	137
PAR1	G $\alpha_{12/13}$	Endothelial cell permeability	138
Thrombin receptor	G $\alpha_{12/13}$	NO production in macrophage	139
Thrombin receptor	G α_{12}	Stress fiber accumulation	140
Thrombin and thromboxane A2	G $\alpha_{12/13}$	Platelet activation	25
Lysophosphatidic acid			
LPA4	G $\alpha_{12/13}$	Limits proper adipose tissue expansion and remodeling in diet-induced obesity	141
LPA4	G $\alpha_{12/13}$	Hypertensive response	122
LPA4/LPA6	G $\alpha_{12/13}$	Angiogenesis	142
LPA receptor	G α_{13}	Stress fiber formation	140
Angiotensin			
AT1R	G $\alpha_{12/13}$	Hyperplasia of cardiac fibroblasts	143
AT1R	G $\alpha_{12/13}$	Vascular endothelial dysfunction	144
Endothelin			
ET _A	G α_{12}	Stress fiber accumulation	140
ATP			
P2Y6	G $\alpha_{12/13}$	Cardiac fibrosis	131
Adenosine			
A1/A2a/A2b/A3	G α_{12}	Fatty acid oxidation	38
Bradykinin			
B2	G α_{13}	Stress fiber formation	140
Serotonin			
5-HT2C	G α_{13}	Stress fiber formation	140
Vasopressin			
V1A	G α_{12}	Stress fiber accumulation	140

Recettori accoppiati a G12/13

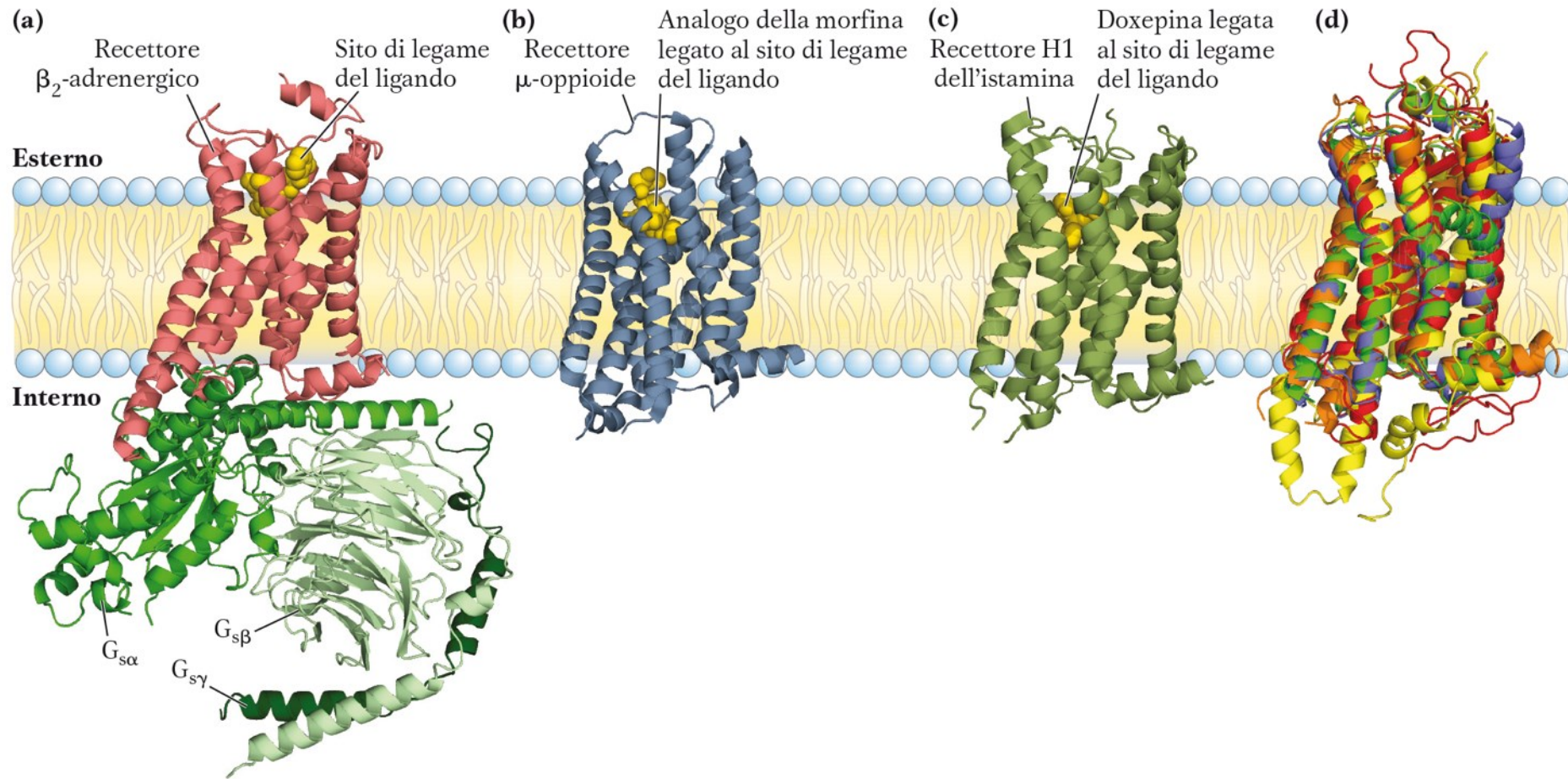




La biosegnalazione via GPCR



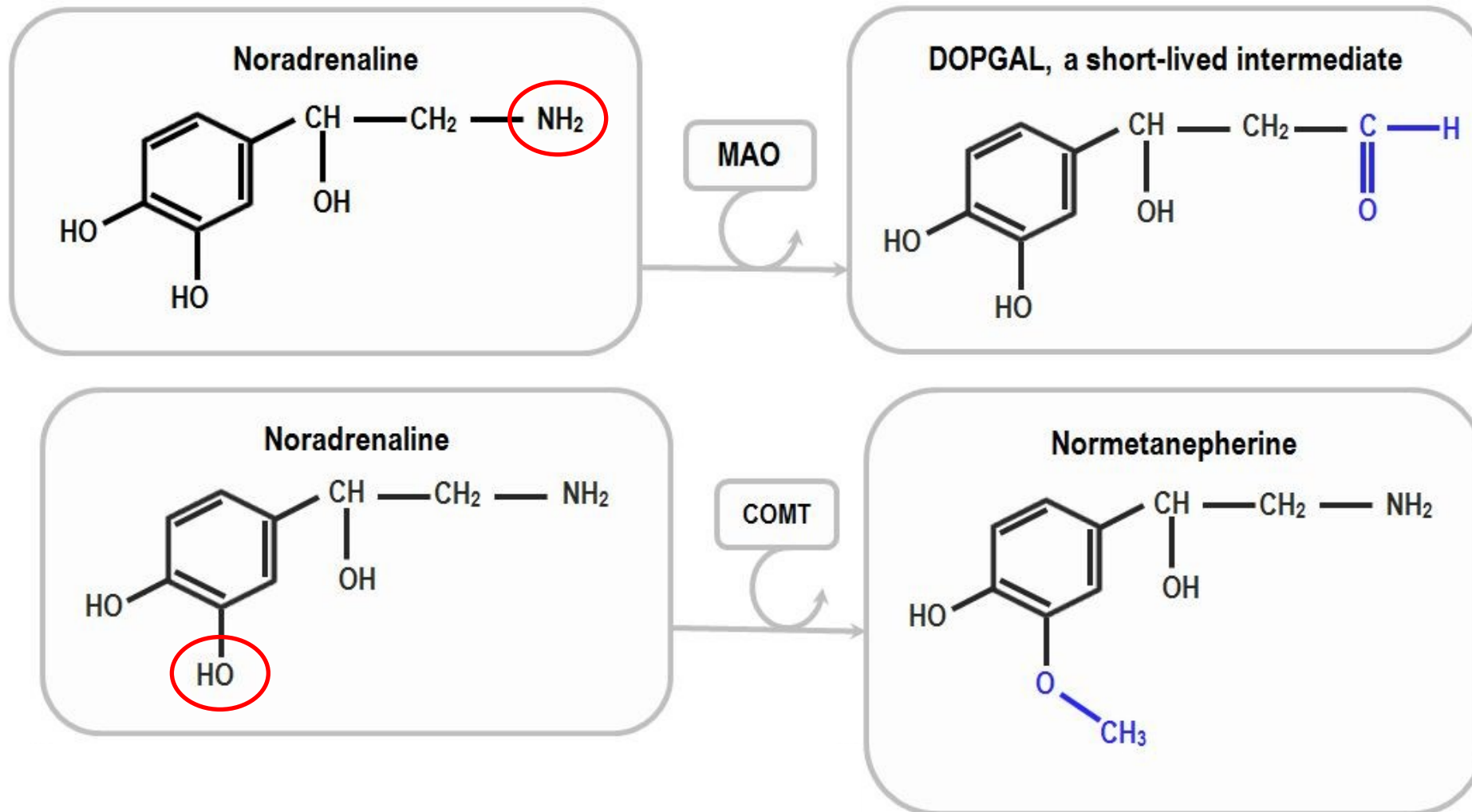
Somiglianze di struttura nei GPCR



Terminazione della risposta

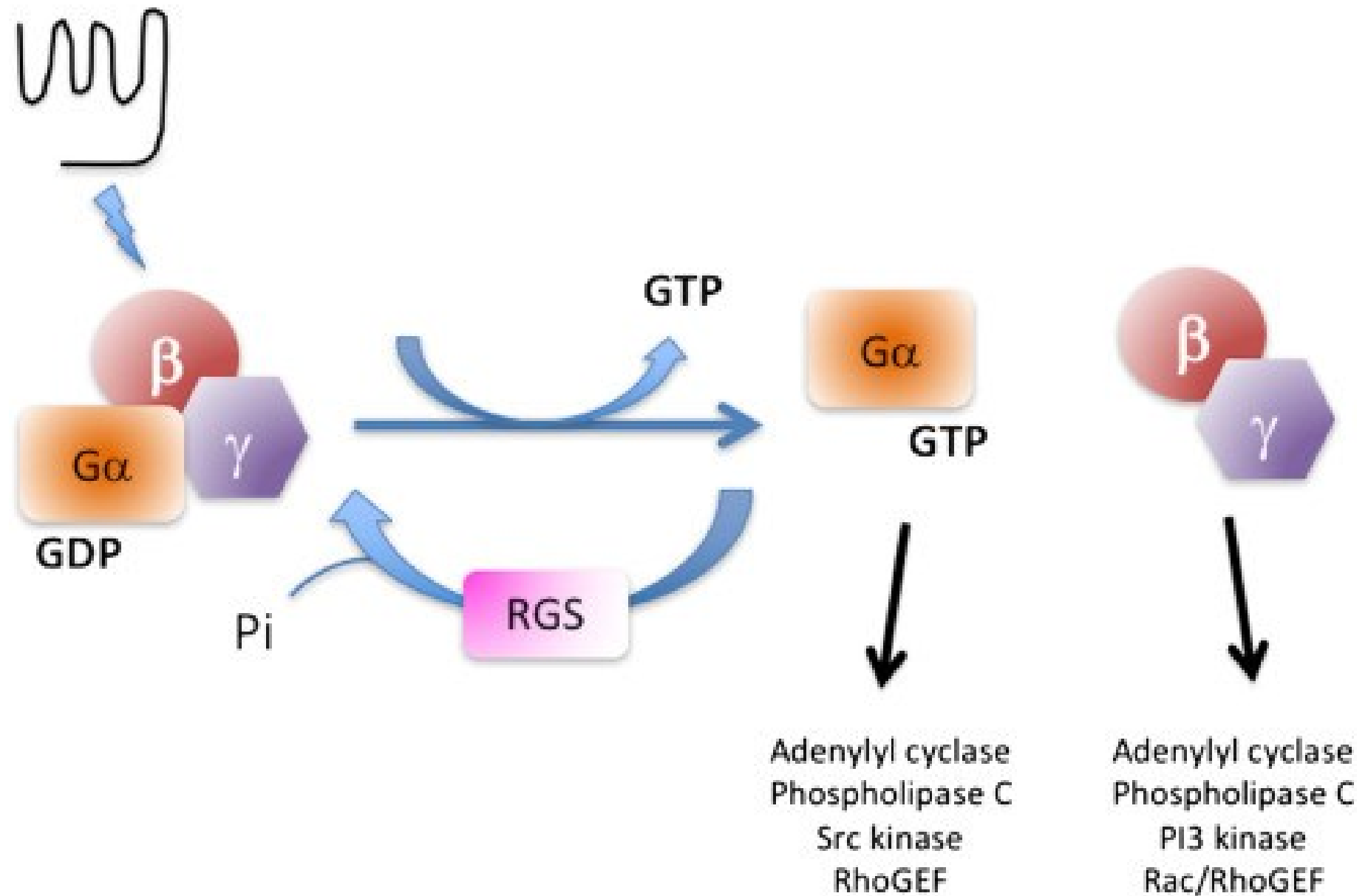
- Re-uptake e degradazione: Monoamino ossidasi MAO e catecol-O-metiltrasferasi (COMT)
- Attività GTPasi intrinseca delle G protein e GAP accessorie (RGS)
- G protein-coupled receptor kinases (GRK), PKA, etc.....
- Arrestins
- Fosfodiesterasi (PDE)/ pompa del Ca²⁺

Azione delle MAO e COMT

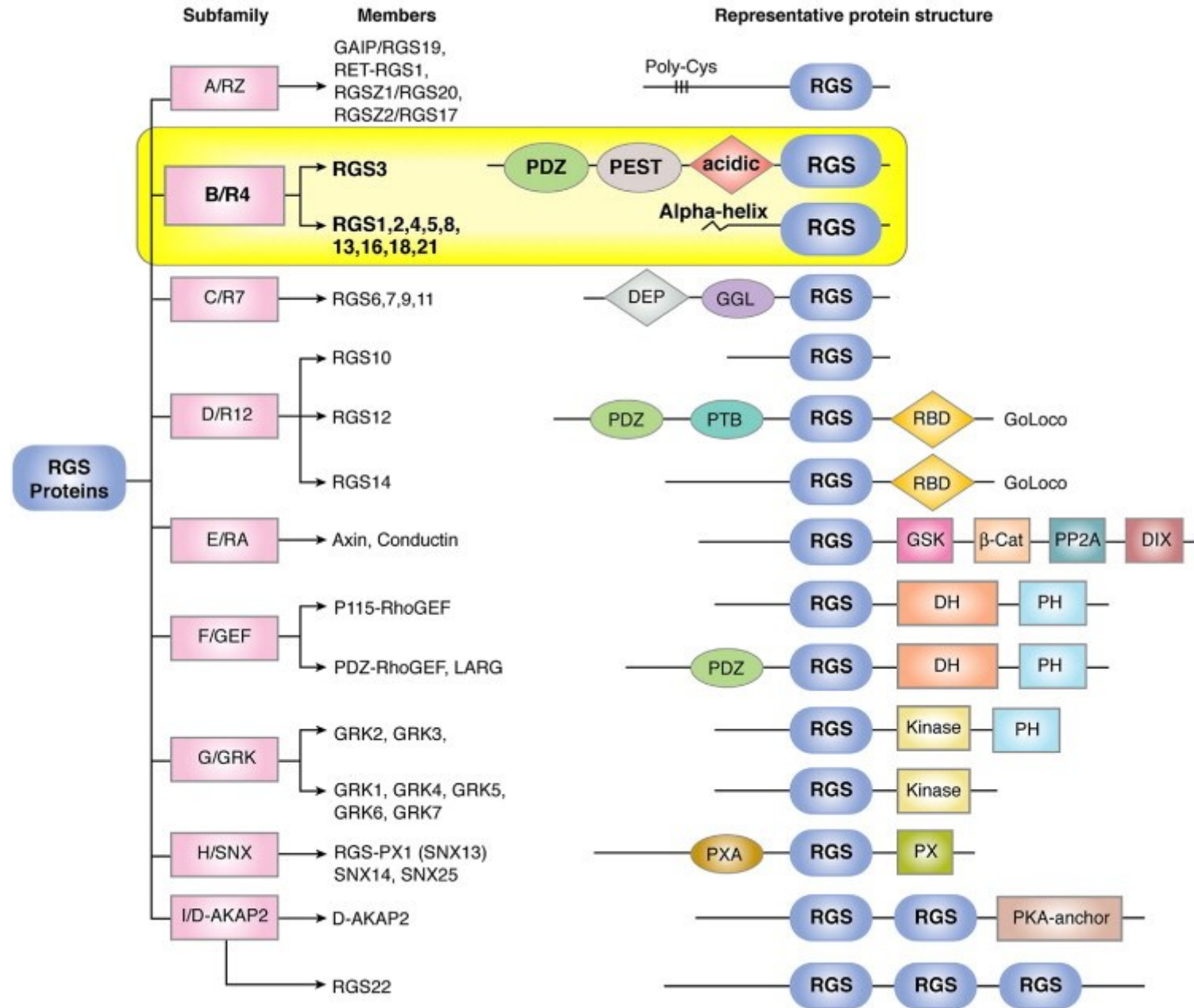


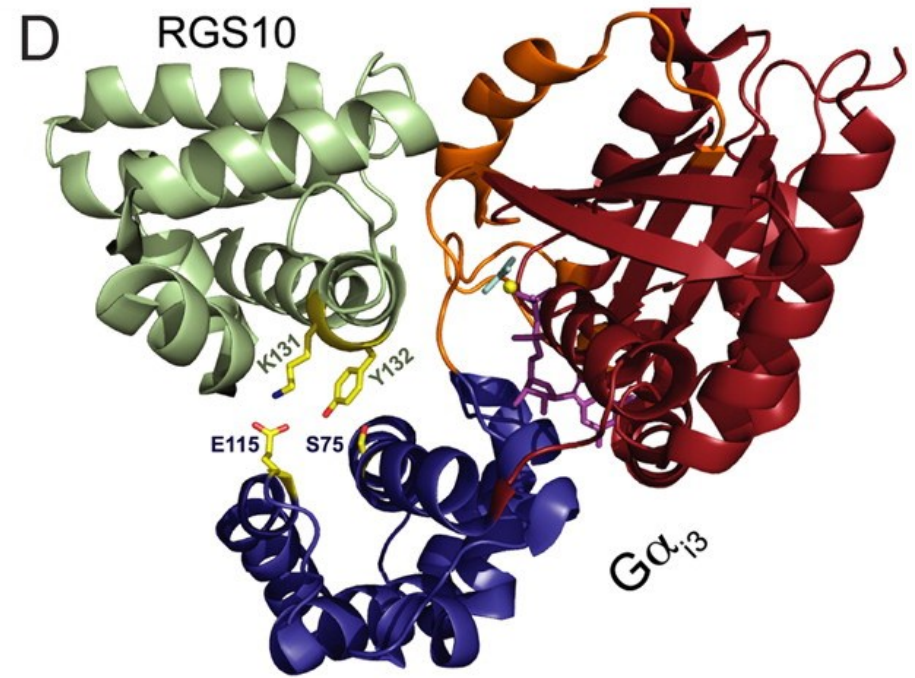
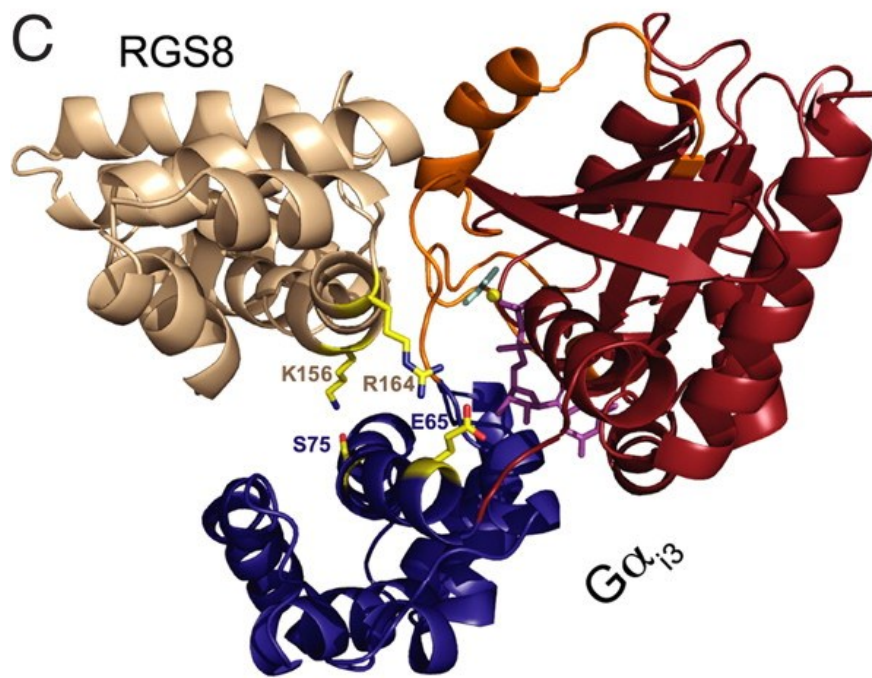
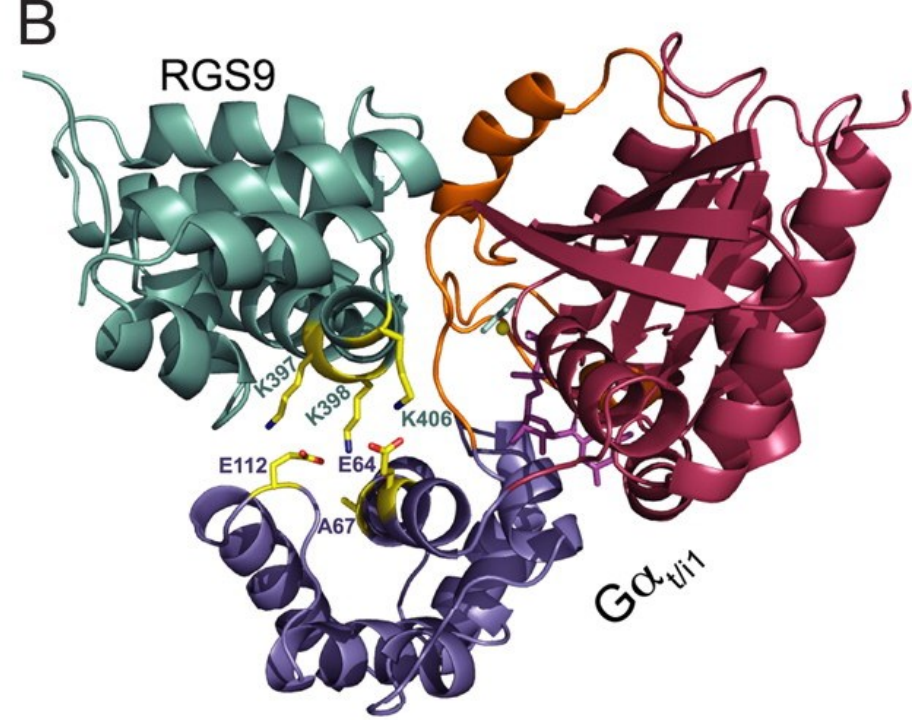
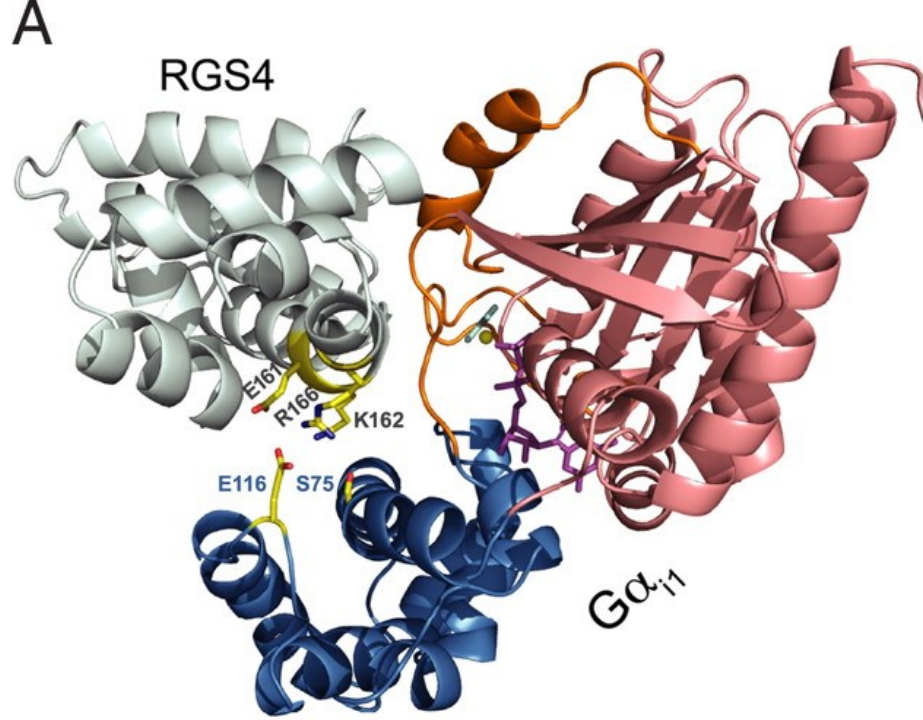
Terminazione della risposta

- Monoamino ossidasi MAO e catecol-O-metiltrasferasi (COMT)
- Attività GTPasi intrinseca alle G protein e GAP accessorie (RGS)
- G protein coupled receptor kinases (GRK), PKA, etc
- Arrestin
- Fosfodiesterasi (PDE)/ pompa del Ca⁺²

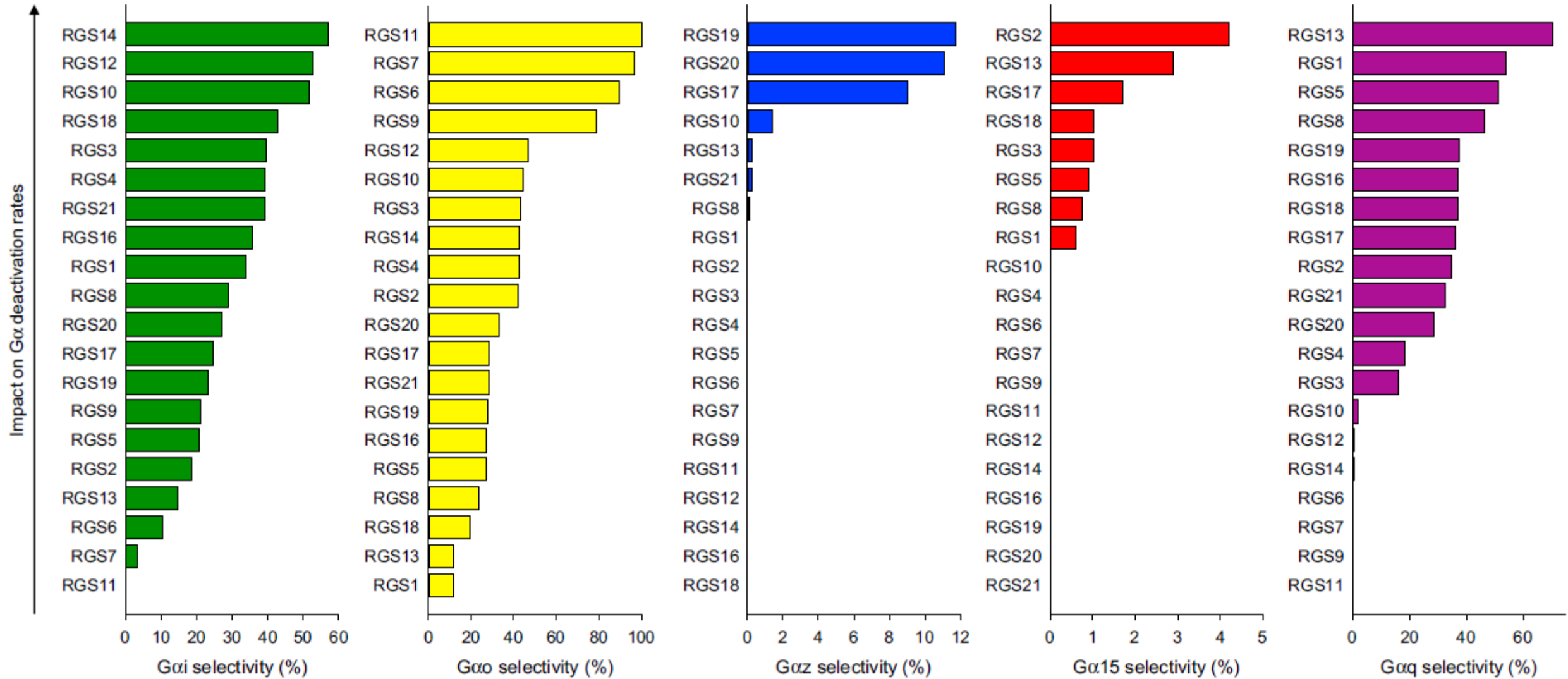


Classification of Mammalian RGS Proteins





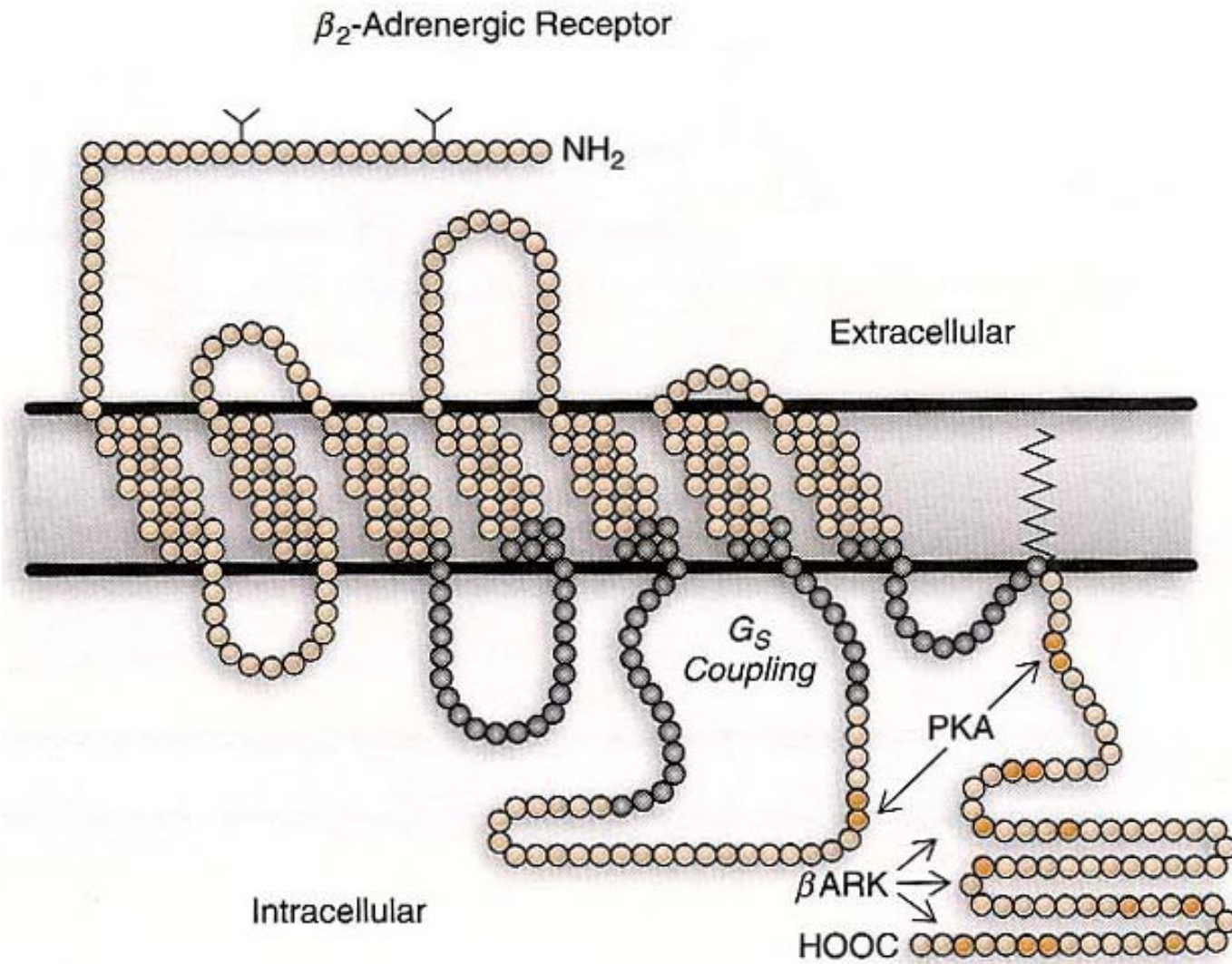
RGS selectivity of G α subunits



Terminazione della risposta

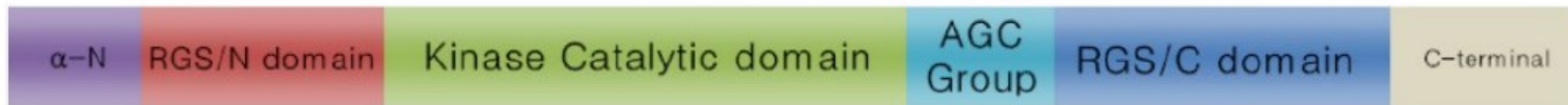
- Monoamino ossidasi MAO e catecol-O-metiltrasferasi (COMT)
- Attività GTPasi intrinseca alle G protein e GAP accessorie (RGS)
- G protein coupled receptor kinases (GRK), PKA, etc
- Arrestin
- Fosfodiesterasi (PDE)/ pompa del Ca⁺²

GPCR desensitization



G protein coupled receptor kinase: GRK

GRK1/GRK7



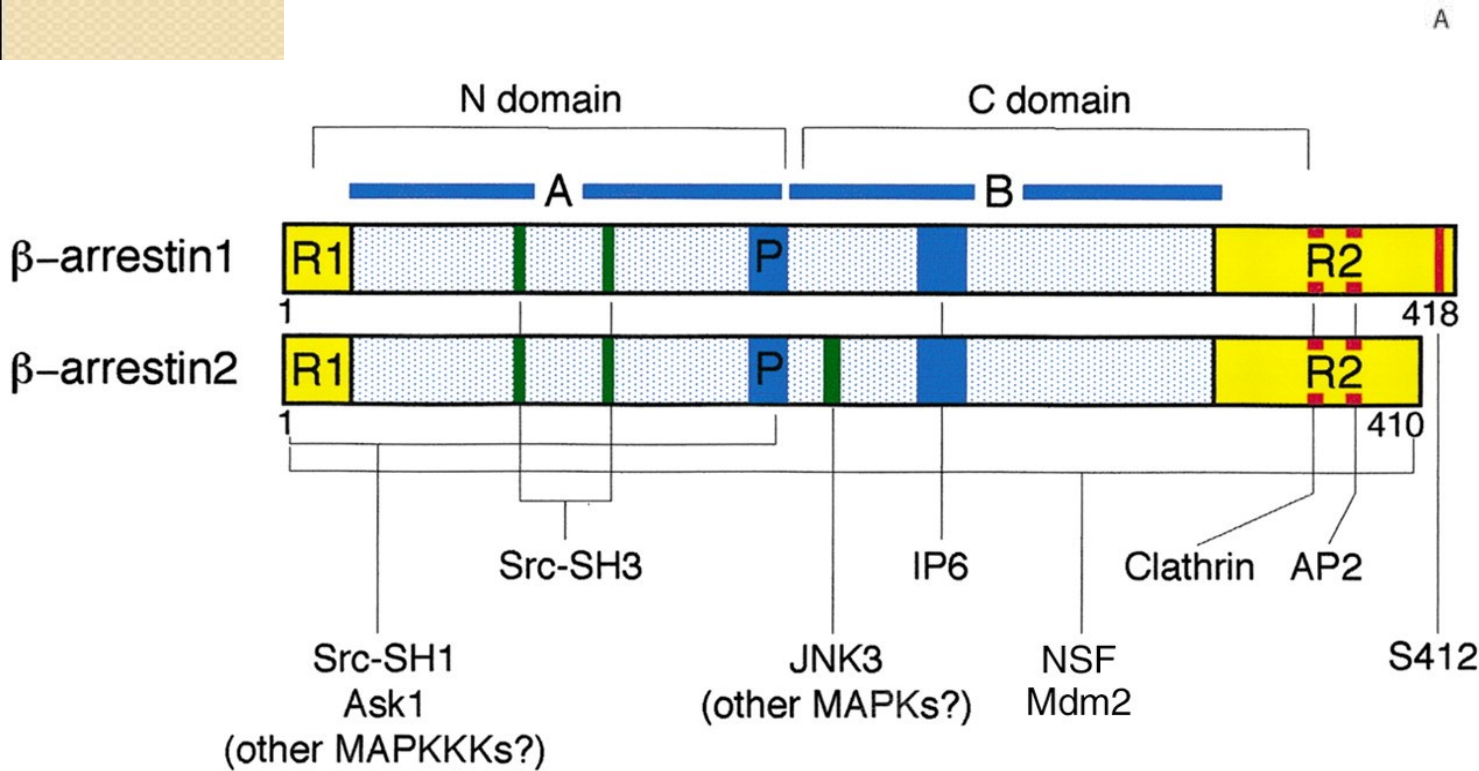
GRK2/GRK3



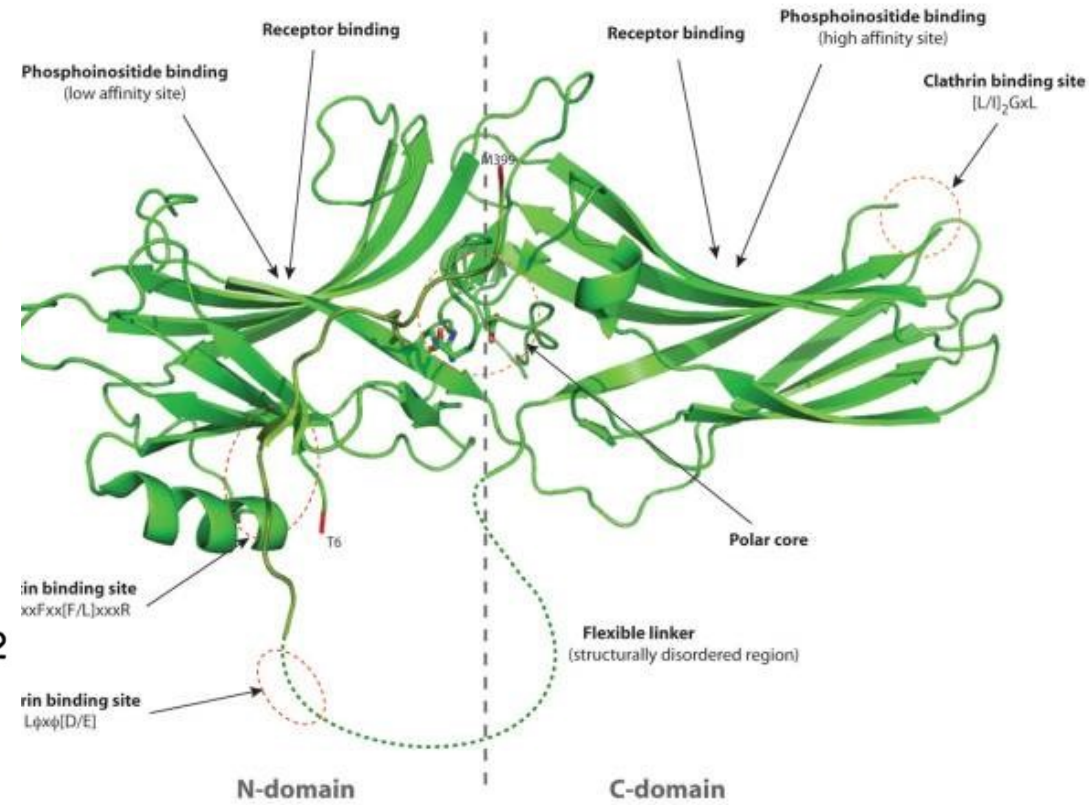
GRK4/GRK5/GRK6



Beta-arrestins

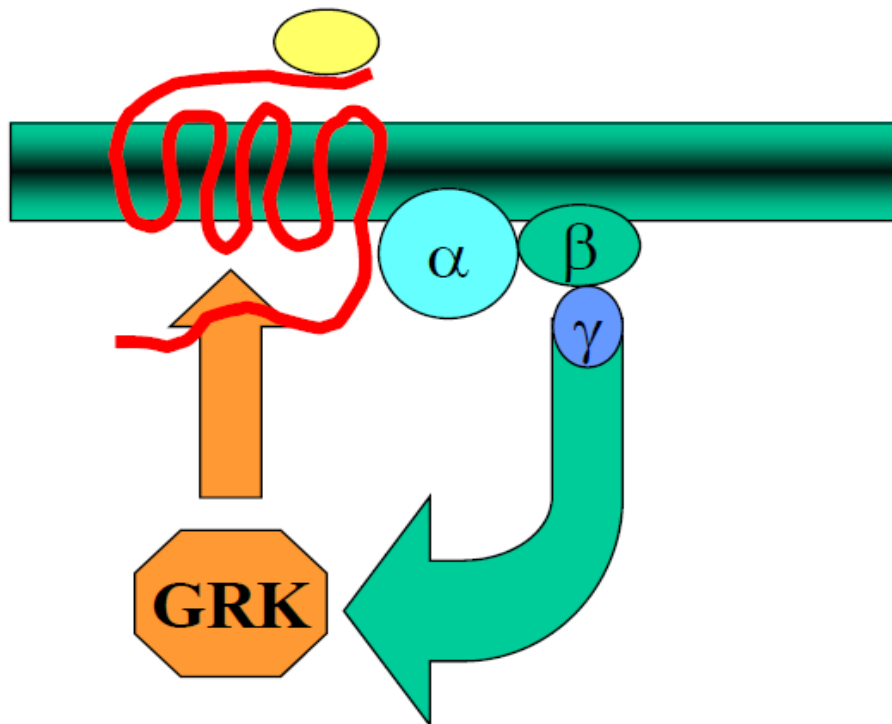


A

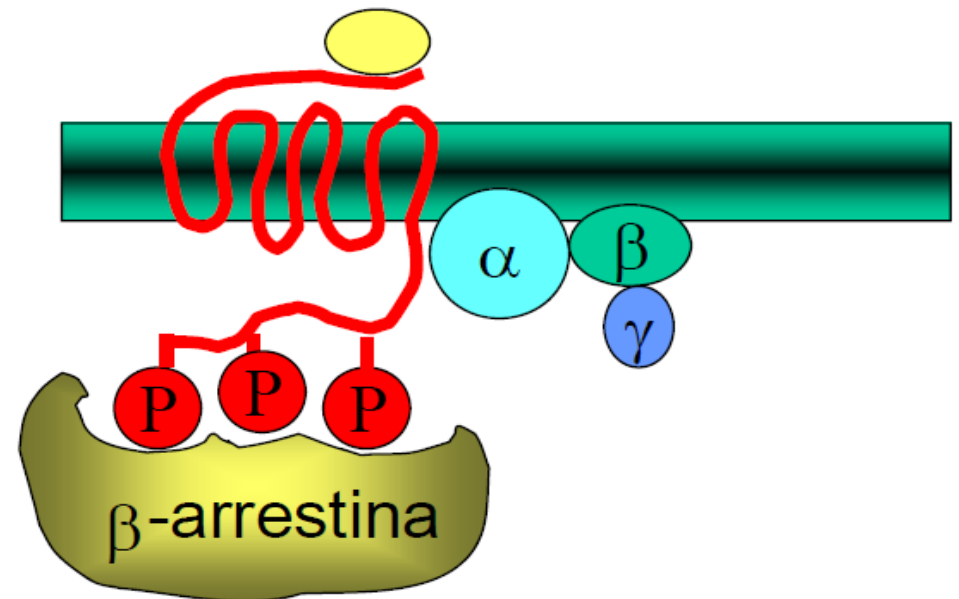


Desensibilizzazione omologa

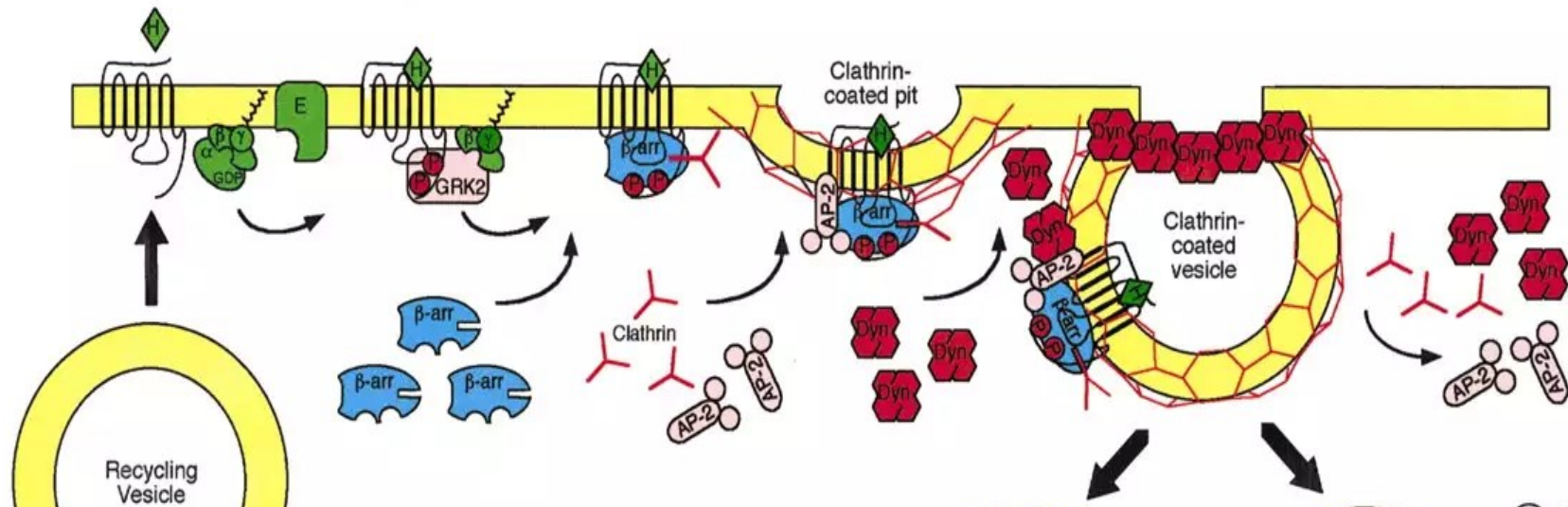
Disaccoppiamento recettore-proteine G in risposta alla **fosforilazione del recettore tramite le GRK** (G protein-coupled receptor kinase) promossa dal dimero $\beta\gamma$



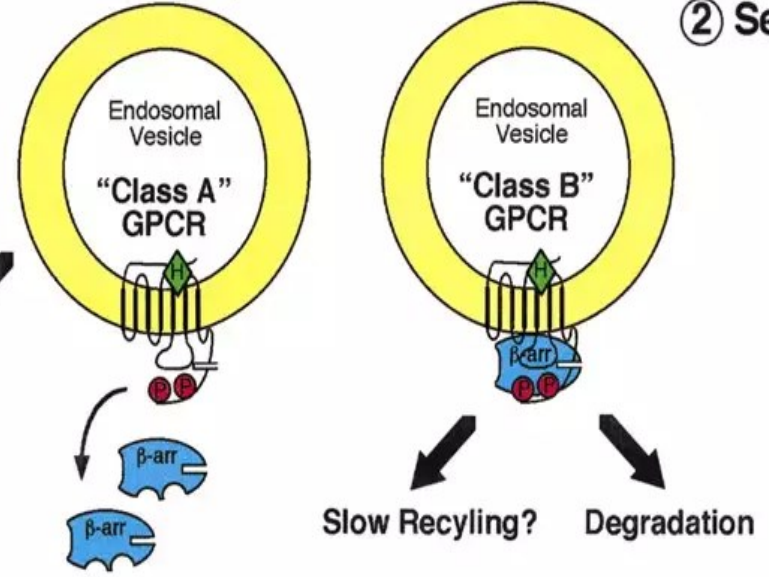
La fosforilazione tramite GRK spesso non è sufficiente per inattivare completamente i recettori; la completa inattivazione richiede un componente aggiuntivo, **l'arrestina**



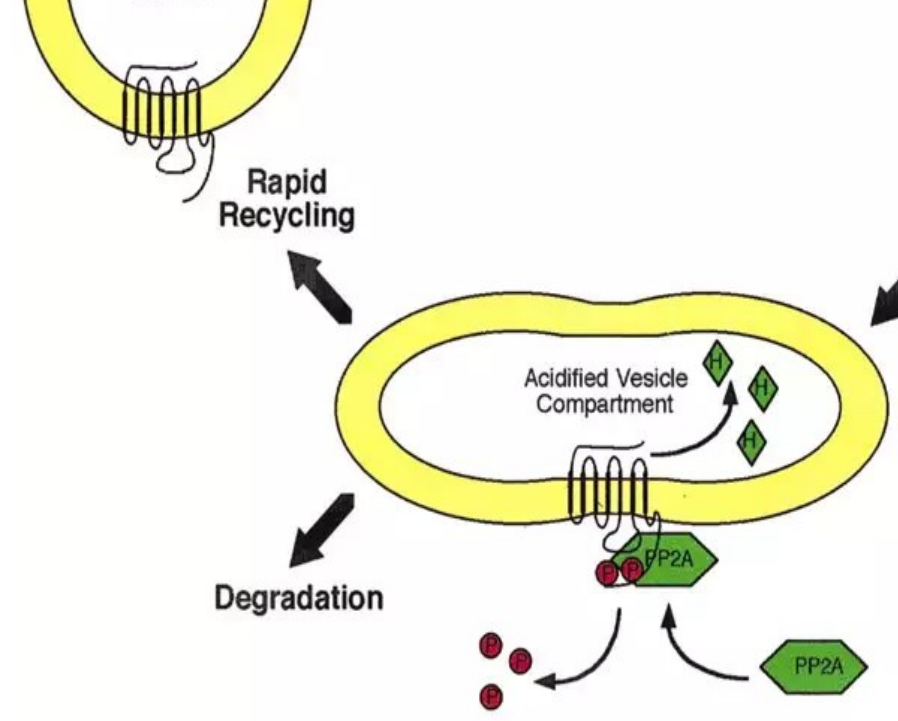
① Desensitization

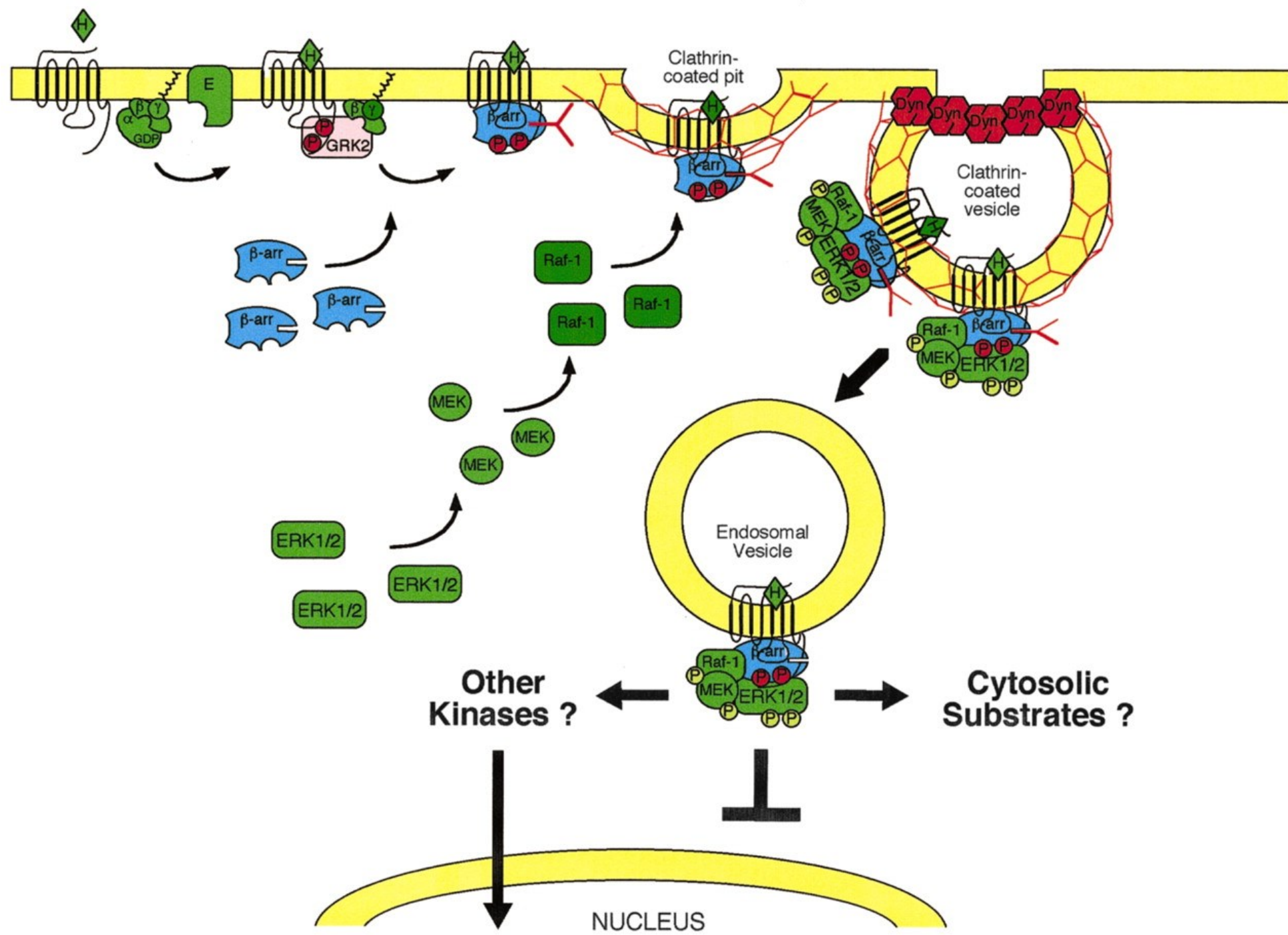


② Sequestration



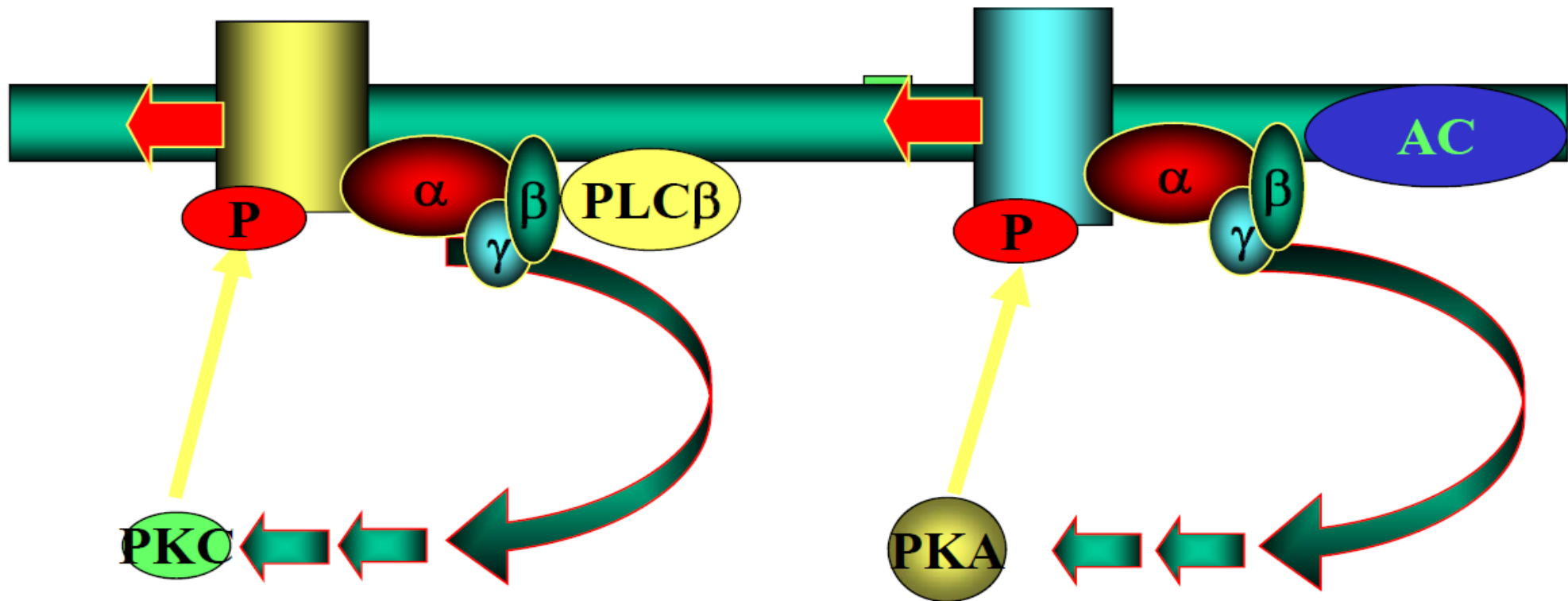
③ Recycling / Downregulation





Desensibilizzazione eterologa

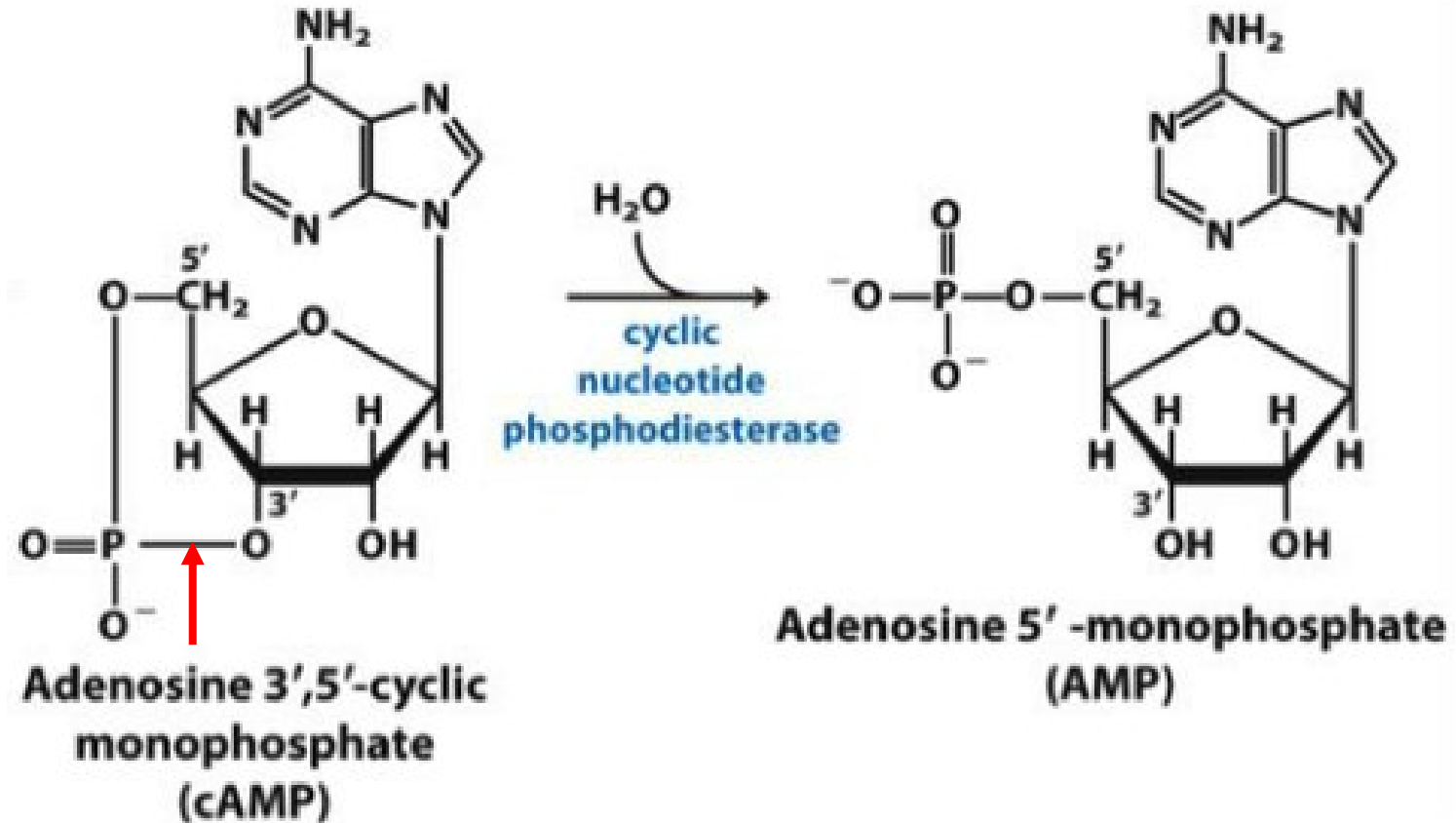
Desensibilizzazione attraverso disaccoppiamento recettore-proteine *G* in risposta alla **fosforilazione del recettore tramite PKA e/o PKC**



Terminazione della risposta

- Monoamino ossidasi MAO e catecol-O-metiltrasferasi (COMT)
- Attività GTPasi intrinseca alle G protein e GAP accessorie (RGS)
- G protein coupled receptor kinases (GRK), PKA, etc
- Arrestin
- Fosfodiesterasi (PDE)/ pompa del Ca⁺²

Fosfodiesterasi



Feed back negativo via fosfodiesterasi

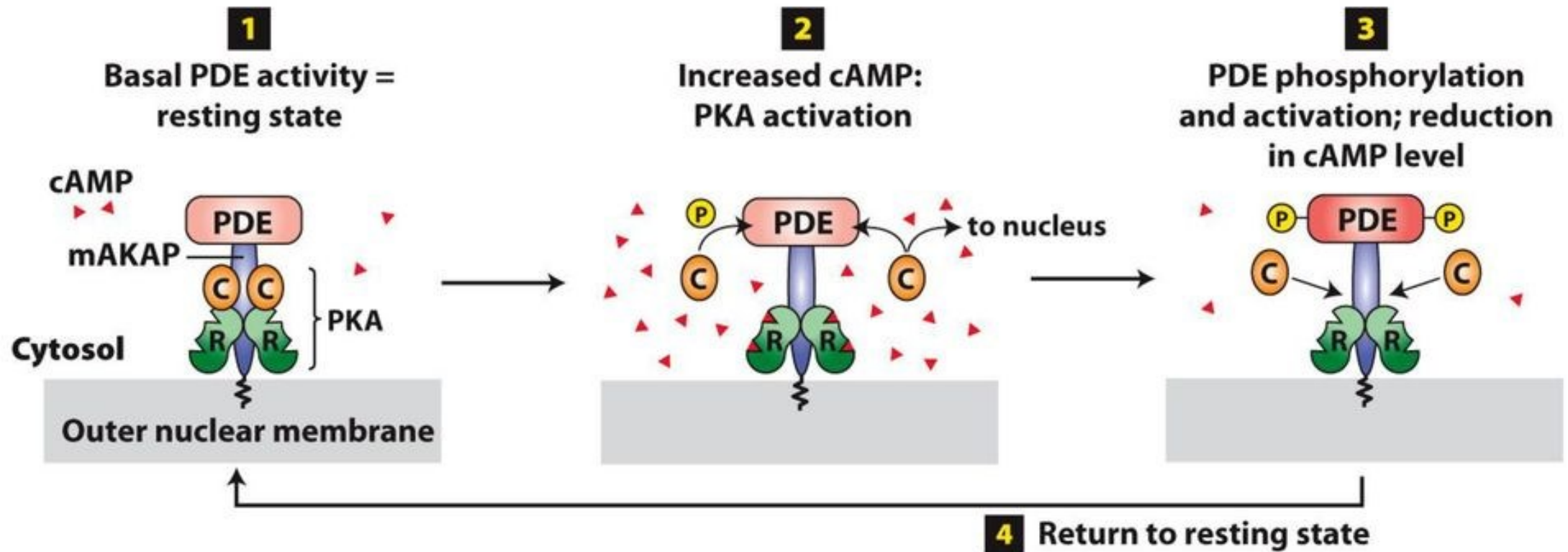


Figure 15-31
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Manoscritti per presentazione studenti

Illuminating G-Protein-Coupling Selectivity of GPCRs

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SUMMARY

Heterotrimeric G proteins consist of four subfamilies (G_s , $G_{i/o}$, $G_{q/11}$, and $G_{12/13}$) that mediate signaling via G-protein-coupled receptors (GPCRs), principally by receptors binding $G\alpha$ C termini. G-protein-coupling profiles govern GPCR-induced cellular responses, yet receptor sequence selectivity determinants remain elusive. Here, we systematically quantified ligand-induced interactions between 148 GPCRs and all 11 unique $G\alpha$ subunit C termini. For each receptor, we probed chimeric $G\alpha$ subunit activation via a transforming growth factor- α (TGF- α) shedding response in HEK293 cells lacking endogenous $G_{q/11}$ and $G_{12/13}$ proteins, and complemented G-protein-coupling profiles through a NanoBIT-G-protein dissociation assay. Interrogation of the dataset identified sequence-based coupling specificity features, inside and outside the transmembrane domain, which we used to develop a coupling predictor that outperforms previous methods. We used the predictor to engineer designer GPCRs selectively coupled to G_{12} . This dataset of fine-tuned signaling mechanisms for diverse GPCRs is a valuable resource for research in GPCR signaling.

complexes, each consisting of $G\alpha$, $G\beta$, and $G\gamma$ subunits, where distinct $G\alpha$ subunits specify both GPCR interactions and the transduction of particular downstream signaling events (Wett- schureck and Offermanns, 2005). The human genome encodes 16 $G\alpha$ genes that are grouped into four subfamilies $G\alpha_s$, $G\alpha_{i/o}$, $G\alpha_{q/11}$, and $G\alpha_{12/13}$ that capture broad properties of downstream signaling (e.g., adenylyl cyclase activation by $G\alpha_s$) (Wett- schureck and Offermanns, 2005). In general, each of the hundreds of mammalian GPCRs couple with more than one G protein giving each a distinct coupling profile (Harding et al., 2018), or signature, which evokes a unique cellular response. Determining these GPCR profiles is critical to understanding their biology and pharmacology.

Pharmaceutical interest in GPCRs has prompted many efforts during the last decades to determine both their ligands and signaling (Hauser et al., 2018). Among approximately 360 non-sensory GPCR genes encoded in the human genome, one-third are still labeled as *orphans* to reflect the fact that either ligands and/or signaling are unknown (Harding et al., 2018). Previous efforts to uncover signaling profiles have been laborious and not standardized yet tended to identify only the subfamily-level signaling outcome (e.g., Ca^{2+} , cAMP, inositol phosphate, Rho activation), rather than the specific $G\alpha$ subunit binding event (Thomsen et al., 2005). Although this has led a collection of data on GPCR ligands and signaling exemplified in the IUPHAR/BPS Guide to Pharmacology (GtoPdb) (Harding et al., 2018), these databases have issues

A Global Map of G Protein Signaling Regulation by RGS Proteins

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SUMMARY

The control over the extent and timing of G protein signaling is provided by the regulator of G protein signaling (RGS) proteins that deactivate G protein α subunits ($G\alpha$). Mammalian genomes encode 20 canonical RGS and 16 $G\alpha$ genes with key roles in physiology and disease. To understand the principles governing the selectivity of $G\alpha$ regulation by RGS, we examine the catalytic activity of all canonical human RGS proteins and their selectivity for a complete set of $G\alpha$ substrates using real-time kinetic measurements in living cells. The data reveal rules governing RGS- $G\alpha$ recognition, the structural basis of its selectivity, and provide principles for engineering RGS proteins with defined selectivity. The study also explores the evolution of RGS- $G\alpha$ selectivity through ancestral reconstruction and demonstrates how naturally occurring non-synonymous variants in RGS alter signaling. These results provide a blueprint for decoding signaling selectivity and advance our understanding of molecular recognition principles.

Receptor Quaternary Organization Explains G Protein-Coupled Receptor Family Structure

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<http://dx.doi.org/10.1016/j.celrep.2017.08.072>

SUMMARY

The organization of *Rhodopsin*-family G protein-coupled receptors (GPCRs) at the cell surface is controversial. Support both for and against the existence of dimers has been obtained in studies of mostly individual receptors. Here, we use a large-scale comparative study to examine the stoichiometric signatures of 60 receptors expressed by a single human cell line. Using bioluminescence resonance energy transfer- and single-molecule microscopy-based assays, we found that a relatively small fraction of *Rhodopsin*-family GPCRs behaved as dimers and that these receptors otherwise appear to be monomeric. Overall, the analysis predicted that fewer than 20% of ~700 *Rhodopsin*-family receptors form dimers. The clustered distribution of the dimers in our sample and a striking correlation between receptor organization and GPCR family size that we also uncover each suggest that receptor stoichiometry might have profoundly influenced GPCR expansion and diversification.

cant structural variation between GPCRs is restricted to the ligand-binding regions, and the parts of the receptors involved in signal transduction are typically much more highly conserved (Katritch et al., 2012), allowing similar conformational changes to accompany receptor activation (Deupi and Standfuss, 2011). Several studies of isolated GPCRs (Bayburt et al., 2007; Ernst et al., 2007; Kuszak et al., 2009; Leitz et al., 2006; Whorton et al., 2007) convincingly show that signal transduction can occur on the scale of single, autonomous receptors, consistent with GPCRs forming 1:1 complexes with G proteins (Rasmussen et al., 2011).

Without question, the most contentious aspect of GPCR biology concerns their quaternary structures. This is not an insignificant issue, as homo- or hetero-oligomer formation offers, e.g., a simple explanation for a wealth of pharmacological data implying that receptors engage in “cross-talk” (although other explanations are possible; Chabre et al., 2009; Tubio et al., 2010) and new opportunities for pharmacological intervention. Whereas several small families of GPCRs comprise receptors whose large N- and C-terminal domains are known to effect dimerization, e.g., the *Glutamate* (class C) receptors (Gurevich and Gurevich, 2008b), there is no consensus regarding the “typical” quaternary structure of the largest group of GPCRs, i.e., the *Rhodopsin* family. It was initially thought that

EGFR Ligands Differentially Stabilize Receptor Dimers to Specify Signaling Kinetics

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<https://doi.org/10.1016/j.cell.2017.09.017>

SUMMARY

Epidermal growth factor receptor (EGFR) regulates many crucial cellular programs, with seven different activating ligands shaping cell signaling in distinct ways. Using crystallography and other approaches, we show how the EGFR ligands epiregulin (EREG) and epigen (EPGN) stabilize different dimeric conformations of the EGFR extracellular region. As a consequence, EREG or EPGN induce less stable EGFR dimers than EGF—making them partial agonists of EGFR dimerization. Unexpectedly, this weakened dimerization elicits more sustained EGFR signaling than seen with EGF, provoking responses in breast cancer cells associated with differentiation rather than proliferation. Our results reveal how responses to different EGFR ligands are defined by receptor dimerization strength and signaling dynamics. These findings have broad implications for understanding receptor tyrosine kinase (RTK) signaling specificity. Our results also suggest parallels between partial and/or biased agonism in RTKs and G-protein-coupled receptors, as well as new therapeutic opportunities for correcting RTK signaling output.

to explain how EGFR family RTKs signal differently in response to their multiple cognate ligands (Sweeney and Carraway, 2000; Wilson et al., 2009).

EGFR is activated by seven different growth factors (Harris et al., 2003), which fall into two groups based on receptor-binding affinity. The high-affinity ligands are EGF, transforming growth factor- α (TGF α), betacellulin (BTC), and heparin binding EGF-like growth factor (HB-EGF), which bind cell-surface EGFR with apparent K_d of 0.1–1 nM. The low-affinity ligands are epiregulin (EREG), epigen (EPGN), and amphiregulin (AREG), which bind 10- to 100-fold more weakly. Numerous studies report distinct EGFR-dependent cellular responses to the different ligands (Wilson et al., 2009), with a given cell line responding differently to individual EGFR ligands in terms of cell proliferation (Wilson et al., 2012), differentiation (Kochupurakkal et al., 2005; Rizzi et al., 2013), and/or motility (Willmarth and Ethier, 2006). Individual EGFR ligands also induce qualitatively and quantitatively different downstream signals (Knudsen et al., 2014; Ronan et al., 2016; Wilson et al., 2012) and are linked to unique phenotypes in vivo (Wilson et al., 2009).

It remains unclear from current mechanistic understanding how different ligands could promote distinct cellular signaling responses through the same RTK. Crystal structures have described how EGF or TGF α induce formation of activated EGFR dimers (Ferguson et al., 2003; Garrett et al., 2002; Kovacs et al., 2015; Ogiso et al., 2002). Our more recent work (Bessman

Bias Factor and Therapeutic Window Correlate to Predict Safer Opioid Analgesics

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<https://doi.org/10.1016/j.cell.2017.10.035>

SUMMARY

Biased agonism has been proposed as a means to separate desirable and adverse drug responses downstream of G protein-coupled receptor (GPCR) targets. Herein, we describe structural features of a series of mu-opioid-receptor (MOR)-selective agonists that preferentially activate receptors to couple to G proteins or to recruit β arrestin proteins. By comparing relative bias for MOR-mediated signaling in each pathway, we demonstrate a strong correlation between the respiratory suppression/antinociception therapeutic window in a series of compounds spanning a wide range of signaling bias. We find that β arrestin-biased compounds, such as fentanyl, are more likely to induce respiratory suppression at weak analgesic doses, while G protein signaling bias broadens the therapeutic window, allowing for antinociception in the absence of respiratory suppression.

induced respiratory suppression (Bohn et al., 1999; Raehal et al., 2005). These findings suggest that activating the MOR without engaging β arrestin2 regulation may be critically important for developing safer opioid analgesics.

A recent development in pharmacological theory and practice is the concept that the structure of a GPCR ligand may be systematically modified to confer alternative receptor conformations upon binding, with each displaying a unique pattern of activation of intracellular signaling cascades (Rankovic et al., 2016; Urban et al., 2007). This concept of functional selectivity, or biased agonism, can be quantified by comparing drug potency and efficacy in cell-based signaling assays to the performance of a reference agonist (a compound that fully activates the system and thus defines the full potential of what one might hope to measure in the assay). Application of the operational model, described by Black and Leff (1983), allows one to simultaneously compare the relative potency and efficacy of a test agonist to the reference agonist, allowing for normalization within an assay (derivation of the parameter: $\Delta\text{Log } \tau/K_A$). After normalization, the performance of the compound can then be compared to its performance within another assay. The result of the comparison can be calculated

Auto-regulation of Secretory Flux by Sensing and Responding to the Folded Cargo Protein Load in the Endoplasmic Reticulum

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<https://doi.org/10.1016/j.cell.2019.01.035>

SUMMARY

Maintaining the optimal performance of cell processes and organelles is the task of auto-regulatory systems. Here we describe an auto-regulatory device that helps to maintain homeostasis of the endoplasmic reticulum (ER) by adjusting the secretory flux to the cargo load. The cargo-recruiting subunit of the coatamer protein II (COPII) coat, Sec24, doubles as a sensor of folded cargo and, upon cargo binding, acts as a guanine nucleotide exchange factor to activate the signaling protein Gα12 at the ER exit sites (ERESs). This step, in turn, activates a complex signaling network that activates and coordinates the ER export machinery and attenuates proteins synthesis, thus preventing large fluctuations of folded and potentially active cargo that could be harmful to the cell or the organism. We call this mechanism AREX (autoregulation of ER export) and expect that its identification will aid our understanding of human physiology and diseases that develop from secretory dysfunction.

optimally despite the physiological and pathological perturbations to which it is exposed. Therefore, it must maintain tight coordination between the transport and processing activities of its main stations—the endoplasmic reticulum (ER), Golgi complex, and endo-lysosomal system—at all times. To date, the cellular mechanisms responsible for this type of coordination remain poorly understood.

In this study, we focus on the first steps in the pathway; namely, the folding and export of secretory cargo from the ER. Here, the fluctuations in protein synthesis that may occur in many cell types (Dolfi et al., 2013; Ron and Harding, 2012; van Anken et al., 2003) could lead to aberrant accumulation of folded and potentially active cargo in the lumen of this organelle, with harmful consequences for the cell or organism. Examples of cargo mislocalization and anomalous activation at the ER, leading to diseases such as cancer, have been reported (Choudhary et al., 2009). Thus, the production of folded cargo proteins in the ER must be coupled with the export process by a mechanism that senses folded cargo and regulates cargo export and synthesis accordingly.

To unravel the expected coordinating mechanism, we developed a strategy based on exposing the ER to a suitable (specific and non-toxic) artificial perturbation designed to induce a synchronous increase of folded cargo in the ER lumen (or “folding

Grazie per l'attenzione

Mechanisms of signalling and biased agonism in G protein-coupled receptors

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Abstract | G protein-coupled receptors (GPCRs) are the largest group of cell surface receptors in humans that signal in response to diverse inputs and regulate a plethora of cellular processes. Hence, they constitute one of the primary drug target classes. Progress in our understanding of GPCR dynamics, activation and signalling has opened new possibilities for selective drug development. A key advancement has been provided by the concept of biased agonism, which describes the ability of ligands acting at the same GPCR to elicit distinct cellular signalling profiles by preferentially stabilizing different active conformational states of the receptor. Application of this concept raises the prospect of ‘designer’ biased agonists as optimized therapeutics with improved efficacy and/or reduced side-effect profiles. However, this application will require a detailed understanding of the spectrum of drug actions and a structural understanding of the drug–receptor interactions that drive distinct pharmacologies. The recent revolution in GPCR structural biology provides unprecedented insights into ligand binding, conformational dynamics and the control of signalling outcomes. These insights, together with new approaches to multi-dimensional analysis of drug action, are allowing refined classification of drugs according to their pharmacodynamic profiles, which can be linked to receptor structure and predictions of preclinical drug efficacy.

Duttilità dei recettori accoppiati alle proteine G

